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In Memoriam

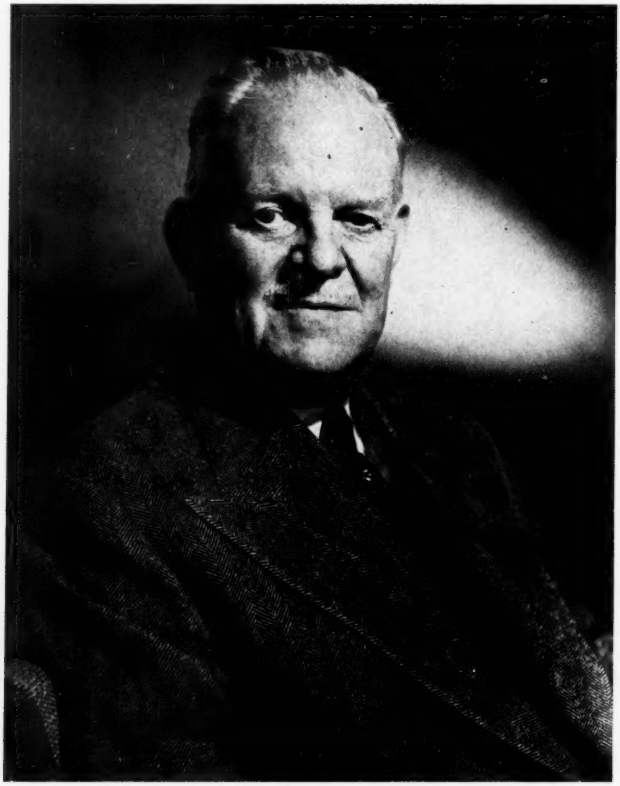
FRANK STEPHEN DOLLEY—1884-1961

ON FEBRUARY 25, 1961, the Southwest lost its pioneer thoracic surgeon with the death of Frank Stephen Dolley. He began his brilliant career in general surgery, confining himself to thoracic surgery in the mid-twenties, as one of the first surgeons in this country to have faith in this budding specialty. He lived to see surgery of the chest develop into a full-fledged specialty, practiced by many surgeons throughout the world, whose techniques and skills have become so complex as to warrant a special board for examination.

Born in Falmouth, Maine, July 26, 1884, Dr. Dolley spent his early boyhood hunting and fishing in the Maine woods and streams, developing a love for outdoors that continued throughout his entire life. When his family moved to California, after the turn of the century, he entered Pomona College, graduating there in 1907; however, he returned to the State of Maine to continue his medical education. He graduated from Bowdoin Medical College in 1911. While there he was given the highest honors in anatomy ever given to a medical student.

Following graduation from medical school he became surgical house officer at Roosevelt Hospital in New York City, and then surgical resident under the training of Dr. George Emerson Brewer who was an established leader in surgery at the Presbyterian Hospital. A Fellowship in Respiratory Physiology under Dr. Haggard at Yale completed the first phase of his formal postgraduate training. An opportunity was presented to return to California, doing part-time teaching at Stanford Medical School and entering into the private practice as Chief Surgeon of the South San Francisco Hospital. During these years of practice of general surgery he came upon an occasional case of thoracic surgical interest. Gradually through the years his interest in thoracic surgery became overwhelming and with great vision for the future he decided to confine his efforts to this phase of surgery.

Plunging into the study of surgery of the chest as a full-time pursuit, he first worked with Dr. Evarts Graham in St. Louis, in both the clinical and experimental fields. A study of lymph flow in the thorax in the experimental laboratory offered new light on this subject. Dr. Dolley then joined Dr. John Alexander's staff at the University Hospital in Ann Arbor, Michigan, where he performed some of the early thoracic surgical procedures that



FRANK STEPHEN DOLLEY

were done in this institution. He and Dr. Alexander visited the major thoracic surgical clinics in Europe where Dr. Dolley stayed on, particularly for study at the Universities of Munich, Heidelberg, and with Professor Sauerbruch in Berlin.

Returning to America in 1929 he settled in Los Angeles to become the pioneer in the Southwest in thoracic surgery. It is of interest that in a speech prepared for the Southwest Medical Association in 1930, he reviewed the latest advances in the field of thoracic surgery both in the United States and abroad. The discussion included the phrenic operation, thoracoplasty

for tuberculosis, drainage of lung abscesses and empyema, and the daring, occasionally indicated, lobectomy for bronchiectasis. Then followed hard work developing services, teaching, and study in Los Angeles where little had been done since the pulmonary experiments of Lemoyne Wills, performed just before the turn of the century, had lain forgotten for many years. Thoracic services were developed by Dr. Dolley at the Los Angeles County General Hospital, White Memorial Hospital, Good Hope Clinic, Veterans Administration Hospital, and Olive View Sanitorium. He contributed particularly to the development of extrapleural pneumothorax for pulmonary tuberculosis, the establishment of graded thoracoplasty for pulmonary tuberculosis, and collaborated as a pioneer in pulmonary resection for this disease. His studies on intrathoracic tumors were noteworthy. He is the author of many articles on surgery.

At the beginning of World War II he collaborated in a series of teaching movies, depicting the management of chest injuries, that were made at the direction of the National Research Council for the use in Army training centers for thoracic surgery throughout the country. These films, made with a tremendous outlay of time and effort, depicted in simple clear-cut fashion the advances in thoracic surgery that had been made between the two wars. They were widely used in Army teaching centers in this country.

Dr. Dolley had the high honor of being elected President of the American Association of Thoracic Surgery and remained as President during the war years. He took an extremely active part in the scientific programs of the Society for over 25 years, served on its committees, and was much loved by the members of the Society during its early intimate, formative years. Following the war he was invited to the Second Congress in Tuberculosis in Argentina in 1949, where he was made an honorary member of the Congress. The same year he lectured extensively in South America. He was a member of many medical and surgical associations in this country and participated in innumerable scientific programs. He was a great teacher. He stimulated many younger men to enter the field of thoracic surgery.

His interests were wide. In addition to hunting, fishing, and ranching, he was a collector of antiques. During the last decade of his life he interested himself in the history of California and, as a member of a number of historical societies, uncovered much original data on the history of the Southwest, particularly that of the Colorado River. Dr. Dolley will long be remembered in the hearts of his medical colleagues and associates and his many patients as a great surgeon, a great humanist, and a great friend.

LYMAN A. BREWER, III

Original Communications

THYMOMA: A CLINICOPATHOLOGIC STUDY

Philip E. Bernatz, M.D., Edgar G. Harrison, M.D. (by invitation),** and O. Theron Clagett, M.D.,* Rochester, Minn.*

A STUDY of thymic tumors must enjoy a prominent but unenviable position in any list of frustrating experiences inherent in the pursuit of medical knowledge. A review of previous publications concerning these tumors reveals a great variation in interpretation of the nature of these neoplasms as well as of their behavior and association of certain clinical syndromes.[1-4] Remarkable as is this dissidence all reports overwhelmingly agree that there is much confusion as well as controversy about this group of tumors. This general philosophy was expressed in a review of experience at the Mayo Clinic in 1950.[5] The present study was initiated with the hopeful ambition that certain gaps in our knowledge of thymic tumors could now be plugged. We are grateful to Blalock and his associates[1] who in 1939 provided an important stimulus to the investigations of the mysteries of the thymus, and it is distressing that with the passing years we have added so little to this report. The thymus remains an enigma and a lack of knowledge of its physiology provides a prominent stumbling block to understanding disease of the thymus. It is hoped this report of 138 patients undergoing operation for thymic tumor at the Mayo Clinic will provide a basis for some conclusions, and, even more important, that it may be a steppingstone to more profitable future investigations.

CLINICAL CONSIDERATIONS

Age and Sex.—The average age of all the patients in this series was 48 years. In noting the extremes in the ages, we find only one child, a boy, 7 years old. The average age of the women with myasthenia gravis and tumor was 43 years which is about 15 years older than the average age of female patients with myasthenia gravis and no tumor who have undergone thymectomy. This is

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likewise true of the males with and without tumor whose respective average ages were 47 and 32 years. The average age of all the patients with thymic tumors without associated myasthenia gravis was 52 years. Thus, as a group, they were older than those with thymoma and myasthenia gravis whose average age was 45 years.

Unlike our patients without tumor undergoing thymectomy for myasthenia gravis among whom the females predominated in a ratio of 2:1, our 138 patients with thymoma were fairly equally divided with regard to the sex. Among the patients without myasthenia gravis in the group there was a slightly larger number of males.

Symptoms.—Seventy per cent of patients without myasthenia gravis in the group had no symptoms from tumor. Patients with myasthenia gravis invariably consulted their physicians because of myasthenic symptoms, and only a few (4) had associated chest pain. Twenty-eight patients with thymic tumor had significant chest pain and, of these, 19 (68 per cent) had invasive tumors to the extent that only biopsy or partial resection could be accomplished. The remaining 9 had particularly large tumors. The ominous import of pain with these tumors was noted in the previous report from this clinic.[5] Dyspnea or symptoms of superior vena caval obstruction or pericardial effusion was infrequently seen in our group but when present these were of ominous significance.

Roentgenologic Appearances.—We have little to add to the discussion by Good in the publication[5] of 1950, from this institution. The thymoma is the most commonly occurring surgical tumor in the anterior mediastinum, but there is little in the roentgenologic appearance to distinguish it for certain from other tumors in this region. The association of myasthenia gravis in a patient with such an x-ray finding is dependable corroborative evidence of a thymic tumor. All preoperative x-ray studies, including multiple views from a variety of angles, were negative in 3 patients in the group who had myasthenia gravis; the tumors were found at exploration for planned thymectomy. In 17 patients (12 per cent) anteroposterior views of the thorax were negative, but a lateral or oblique view revealed the tumor.

In approximately 10 per cent of the entire group some type of calcification was noted in the roentgenograms. If the calcification was linear in nature and peripheral in location, it was invariably found in the wall of a noninvasive cystic thymoma or in the fibrous capsule of a well-demarcated tumor. Such linear calcification may give a strong impression of aortic aneurysm on some views, but this lesion can usually be excluded without arteriographic studies. Whereas peripheral linear calcification was indicative of a favorable type of tumor, scattered calcification was seen in some growths which proved to be beyond resection with implants on adjacent pleural surfaces.

The thymic tumor which is usually sharply demarcated is seen almost exclusively in the anterior mediastinum at the base of the heart, but it may occur at any level from the neck to the diaphragm. In one case reported from the clinic[6] the only demonstrable thymic tumor was confined to the middle lobe of the right lung. The tumor may largely maintain the configuration of the

thymus and, therefore, may be difficult to demonstrate roentgenologically; others have presented other problems by being so large that they are difficult to recognize as originating in the anterior mediastinum.

ASSOCIATED CLINICAL SYNDROMES

Myasthenia Gravis.—Of these 138 patients with thymic tumors, 64 (46 per cent) had associated myasthenia gravis which is considerably different from the 70 per cent recorded in the earlier report of our experience at this clinic. This difference can be explained easily by the larger number of asymptomatic thymic tumors found on routine roentgenograms of the thorax in the present group. The incidence of association with myasthenia gravis is likely to continue downward in our future series as our earlier experience becomes diluted. It seems reasonable to presume that myasthenia gravis and thymic tumor are related, but we have little beyond circumstantial evidence to support this premise.

It is not possible from our clinical review to say that myasthenia gravis associated with thymic tumor is a different disease from myasthenia gravis without thymoma. The patients are a little older, and the predominance of young females is less evident, but we cannot support with any certainty the suggestion that myasthenia gravis when associated with tumor is particularly abrupt in onset or has a more malignant course.[4]

Predictability for influencing the myasthenia gravis by excision of the tumor has been fraught with uncertainties. In 1939, Blalock and associates[1] referred to a cystic tumor of the thymic region which could not be positively recognized as being thymic in origin, yet removal was associated with the amelioration of symptoms of myasthenia. It has been generally contended by ourselves[5] and others that surgeons could not hope to influence the course of patients with myasthenia gravis by excising a thymoma, and surgical indications, therefore, were primarily based on the lethal potential of the neoplasm itself.

The course of the 64 patients with myasthenia gravis in our series suggests that we modify this thinking. Eleven patients are completely well and receiving no medication, the average period following operation in this group being 8 years, with extremes of 2 and 17 years. An additional 7 patients are well and normally active, although they are receiving medication. Eight patients are severely disabled with myasthenia gravis and the remainder have died, were not traced, or were operated upon too recently to evaluate. Thus, the myasthenia gravis of 18 of these patients (28 per cent) was definitely benefited after operation. The sex and age of this group did not indicate that young females were benefited especially, as they are in 68 per cent of instances in which thymectomy is performed for myasthenia gravis without thymoma.

When one considers that only a few patients with myasthenia gravis enjoy prolonged spontaneous remissions, there is room for some enthusiasm on noting these results even though the number of patients is too small for dogmatic conclusions. We cannot say that complete excision of the thymus with the tumor has necessarily made a difference, but we would urge that this be done in every instance if possible.

In one of the 138 patients, myasthenia gravis began after removal of a thymic tumor. The onset was 3 years after operation, and death resulted subsequently. In a review of the literature in 1957, Rowland and associates[7] reported 10 cases in which myasthenia gravis became evident after excision of thymic tumors.

Agenesis of Erythrocytes.—The association of thymic tumor and agenesis of erythrocytes has been recorded in at least 17 patients.[8] Experience at the clinic with 2 cases was reported previously,[9] and a third case has been encountered since this report. Myasthenia gravis with agenesis may be associated; the myelopoietic system is generally unaffected but may be affected, platelets are usually normal, and reticulocytes are much reduced in number or are absent. Six of the patients whose cases have been reported in the literature have benefited from removal of the thymoma: 4 had early erythrocytic responses, and 2 had late responses. One of our own patients did not improve until 2 years after operation. Then anemia decreased with parenteral administration of testosterone by his physician. The other 2 had no beneficial hematologic effects from excision of their thymic tumors. Predominant cell types have not been consistent in all reported cases, but in our 3 cases the tumors were well-encapsulated and of the spindle cell type. The complexity of the association is increased by reports of depression of marrow elements other than erythrocytes and the implication of malignant thymic tumors.[8, 10] The relationship appears to be more than one of chance, but the mechanism remains an enigma. At present our only partially effective treatment has consisted of some combination of thymectomy or excision of the tumor, splenectomy, and administration of steroids and hormones, and it is difficult to pin point the most effective maneuver. Although a sufficient clinical trial has not been completed, thymectomy has not proved effective in the treatment of similar anemia without tumors of the thymus.[8]

Acquired Agammaglobulinemia.—Agammaglobulinemia was not recognized in any of our 138 cases. Whether such an association is chance is questionable since Gafni and associates[11] have reported several cases of idiopathic acquired agammaglobulinemia associated with thymoma. With present laboratory methods we might discover this protein disturbance more frequently if we pursued it more diligently in every patient with thymic tumor, regardless of the absence of significant clues. In the few patients with this combination treated with operation the results have not been uniformly beneficial.

Some workers have suggested that the thymus is an important source of a protein substance that may be a gamma globulin and that numerous hyperglobulinemic conditions may be dependent on the thymus for this protein constituent.[12] MacLean and associates[13] were unable to demonstrate that the thymus participates in the immune response in rabbits.

As in the problem of associated agenesis of erythrocytes, we lack a basic knowledge of thymic function and as a result there is confusion in the formulation of concepts of pathophysiology. The association of thymic tumors and agammaglobulinemia should stimulate further research on the "mythical" function of the thymus.

Cushing's Syndrome.—Experience with thymic tumors associated with Cushing's syndrome at our clinic was reported by Scholz and Bahn,[14] but these were necropsy cases. This association was not noted in our 138 patients with thymic tumor coming to surgery. At the time of their report, 11 similar cases had been reported in the literature. Castleman[2] noted a consistent microscopic appearance in tumors from such patients with a predominance of epithelial cells in a pattern similar to that in tumors from patients in Scholz and Bahn's report in which a glandular or cylindromatous epithelial pattern was noted. The high mortality in reported cases has led to the suggestion that excision of the mediastinal tumor be delayed until Cushing's syndrome is well controlled.

PATHOLOGIC FEATURES

Definition.—Thymoma is a generic term designating a tumor of the thymic parenchyma composed of epithelial (reticuloepithelial) cells and lymphocytes (thymocytes) in variable proportions.[5, 15] The term was first applied by Grandhomme to tumors of this structure.[16, 17] Some confusion in the scope of this designation has resulted from the inclusion of various tumors which may be seen in the region of the mediastinum, for example, teratomas, seminomas, lymphomas, especially in Hodgkin's disease, and metastatic malignant neoplasms. These lesions are excluded from this discussion. Certain benign tumors[2] may mimic thymomas. These include thymic hyperplasia, thymolipoma, hyperplastic mediastinal lymph nodes, and thymic cysts of developmental, lymphatic, or hassallian origin, none of which is included in this series either.

Material Studied.—The material available for review consisted of all surgically removed or biopsied thymomas seen at this institution up to Jan. 1, 1961. Ninety-six gross surgical specimens were available for study. In addition, the original microscopic slides in all 138 cases were reviewed. Sections from three to four blocks of tissue from these 96 gross surgical specimens and available biopsy material from invasive tumors were prepared and stained with hematoxylin and eosin. Selected sections were also stained by the periodic acid-Schiff method and by Gomori's reticulum stain.

Classification of Thymomas.—A number of classifications have been offered for thymomas (Table I). The two basic thymic elements, epithelial cells and lymphocytes, may present a bewildering array of combinations, and thus complex subdivisions have evolved from these variable patterns. This has led to more confusion than accord concerning nomenclature. However, as Lattes and Jonas[24] pointed out, a theme running through the literature suggests some harmony in classification based on the predominant cellular composition. One cannot deny an element of discord in any classification based on predominant cell type when a completely mixed histopathologic form is found, such as an even blending of epithelial and lymphocytic elements, or, less frequently, relatively pure islands of one cell type in a basic background of another. With the hope that some prognostic significance could be gained through study of cell types, as is apparently true in bronchogenic carcinoma,[26] our material was

divided according to the predominance of lymphocytic, epithelial, spindle, and mixed cell types (Table I), and a study was made of any differences in morphology or behavior noted in the several categories.

Gross Findings.—The thymoma has certain distinctive features (Figs. 1 and 2). The foremost feature, as seen in three fourths of the present group of noninvasive tumors, is usually an ovoid or flattened discoid, bosselated tumor showing through a fibrous capsule of variable thickness. The cut surface is often

TABLE I. TEN CLASSIFICATIONS OF THYMIC TUMORS

1. *Symmers,[18] 1932*
- Perithelioma
- Lymphosarcoma
- Epithelioma
- Spindle cell sarcoma
- Hodgkin's disease

2. *Ewing,[19] 1940*
- Lymphosarcoma (thymoma from reticulum cells)
- Carcinoma of reticulum cell origin
- Myxosarcoma

3. *Hellwig,[20] 1941*
- Lymphosarcoma
- Leukosarcoma
- Hodgkin's disease
- Carcinoma

4. *Lowenhaupt,[21] 1948*

Group
- I. Carcinoma of primitive epithelial reticulum
- II. Carcinoma of variegated cell pattern (carcinoma of early Hassall's corpuscles, with or without abortive Hassall's corpuscles)
- III. Carcinoma of granulomatous pattern (carcinoma of late Hassall's corpuscles: thymic Hodgkin's disease)
- IV. Carcinoma of thymic round cell: lymphoepithelioma
- V. Encapsulated thymoma
- VI. Carcinoma of adamantinomatous pattern

5. *Seybold, McDonald, Clagett and Good,[5] 1950*
Castleman,[2] 1955
Iverson,[22] 1956
- Thymoma
  - Without myasthenia gravis
  - With myasthenia gravis

6. *Effler and McCormack,[3] 1956*
- Lymphomatous type
  - Lymphocytic variant
  - Hodgkin's variant
- Carcinomatous type
  - Lymphoepithelial
  - Epithelial variant

7. *Thomson and Thackray,[23] 1957*
- Epithelial
  - Differentiated or epidermoid
  - Oval or spindle cell
  - Lymphoepithelioma
  - Granulomatous
  - Undifferentiated
- Lymphoid
- Teratomatous

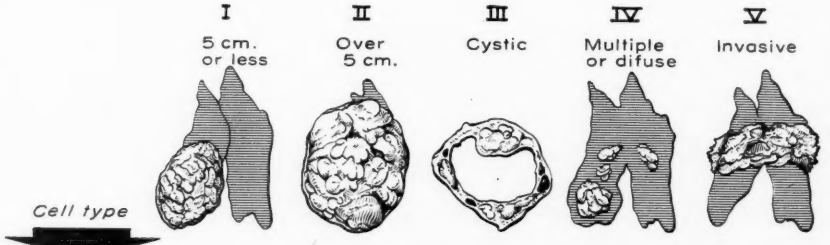
8. *Lattes and Jonas,[24] 1957*
- Predominantly lymphoid
- Predominantly spindle cell with cribriform areas
- Predominantly epithelial in sheets and cords
- Rosette forming type
- So-called granulomatous type
- So-called seminoma type

9. *Andritsakis and Sommers,[25] 1959*
- Thymic tumors
  - Epithelial
    - Undifferentiated
    - Reticular
      - Spindle cell
      - Clear cell
    - Trabecular
    - Epidermoid
    - Glandular
    - Adenoacanthomatous
  - Lymphoid
  - Embryonic
  - Fatty
  - Cystic
  - Hyperplastic

10. *Bernatz, Harrison, and Clagett**
- Thymoma
  - Noninvasive
  - Invasive
    - Predominantly lymphocytic type
    - Predominantly epithelial type
    - Predominantly mixed type
    - Predominantly spindle cell type

*Present study.

grayish-pink to yellow, nodular, or compartmentalized by gross fibrous trabeculae. This was noted in 92 per cent of our specimens. These trabeculae may be thin or broad and converge into irregular fibrous or cystic zones. Cystic formation is frequently a minor feature of the larger tumors. In 24 per cent of our specimens without invasion, however, the tumor was almost completely cystic, and at times only remnants of thymoma, sometimes seen as mural nodules, could be found in a fibrous wall. The contents of the cysts varied from necrotic, hemorrhagic, and fatty, semisolid grumous material to serous fluid. Occasionally, gross calcification was seen in the walls of cysts or in focal deposits in fibrous zones, and punctate hemorrhages were noted on the cut surface.



Cell type	I	II	III	IV	V
Lymphocytic	12	9	9	0	9
Epithelial	2	4	3	0	10
Mixed	4	9	6	1	16
Spindle	3	17	2	2	5
Total	*21*	*39*	*20*	*3*	*40*

Fig. 1.—Gross features of thymomas which were available for gross study, correlated with predominant cell types. Cases in which biopsy only was performed are included in Group V.

In the current series, the size of predominantly solid tumors varied from 15 cm. in maximal dimension with a weight of 915 grams to 3 cm. and a weight of 36 grams. Predominantly cystic tumors varied in size from 15 to 5 cm. In about 8 per cent of gross specimens available for review, the tumor had no gross trabeculae and presented a homogeneous, smooth or granular cut surface. The growth sometimes replaced the entire thymus; at other times, it was confined to one lobe of the gland. A third of predominantly solid, noninvasive tumors were 5 cm. or less in maximal dimension. The majority of the thymomas of lymphocytic type were small, whereas those of spindle cell type were frequently large, although usually well encapsulated. All types were represented in the cystic tumors. In three instances multiple separate nodules of thymoma were distributed in the thymus. This unusual gross form may be an expression of multicentric development from thymic lobules or extension of the tumor. Invasive tumor could not be distinguished grossly from circumscribed neoplasm except by its ragged appearance or the obvious infiltration of a portion of the adjacent structures. The epithelial and mixed cell types were more often associated with invasive growth than were the spindle and lymphocytic cell types.

Microscopic Findings.—1. *Thymoma of predominantly lymphocytic type:* Most classifications have included a subvariety of thymoma characterized by lobular formations predominantly composed of mature lymphocytes with only a scattered background of reticuloepithelium, as was true in 30 per cent of our series (Fig. 3, *a* and *b*). The lymphocytic lobules in this type were usually more angular and less rounded than in the other types and were separated by thin fibrous trabeculae often made up of mature collagen. Epithelial cells were present as scattered cells overshadowed by the lymphocytic predominance.

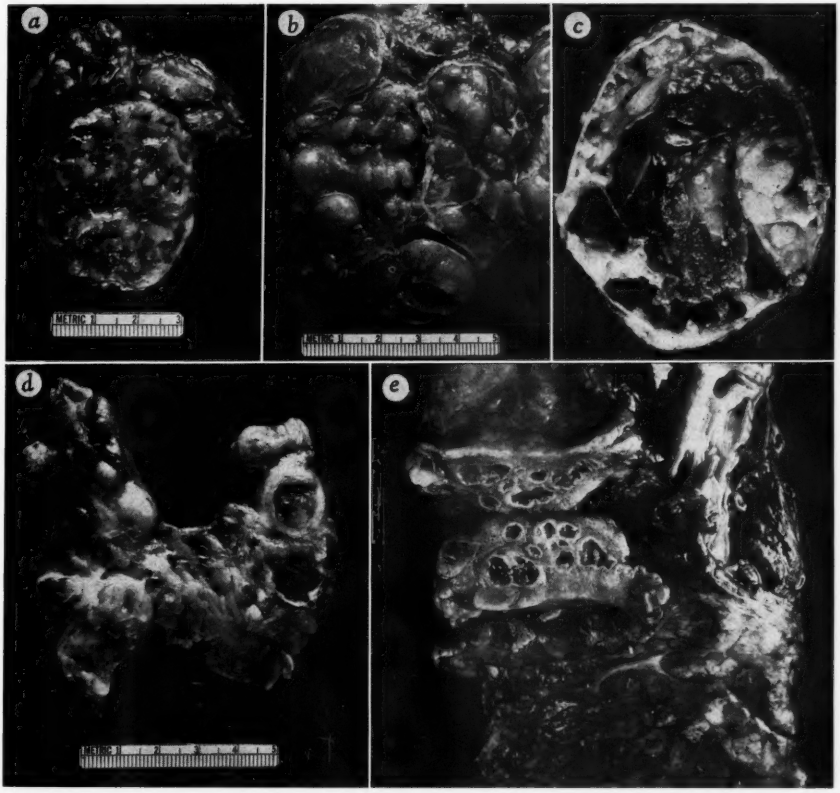


Fig. 2.—Thymomas; four major gross types. *a*, Predominantly lymphocytic type of thymoma which is less than 5 cms in diameter and arises eccentrically from the thymus. The patient had myasthenia gravis. *b*, Thymoma (predominantly spindle cell type) which is more than 5 cm. in diameter and has almost replaced the thymus. Note nodularity and gross trabeculae. The patient had aregenerative anemia without myasthenia gravis. Only half of the tumor is shown. *c*, Cystic thymoma (predominantly spindle cell type) which has only mural nodules of viable tumor. The patient did not have myasthenia gravis. *d*, Multiple or diffuse thymoma (mixed type). Patient had myasthenia gravis. *e*, Invasive thymoma (predominantly epithelial type) infiltrating lobe of lung. The patient had myasthenia gravis.

They usually were seen as isolated cells or in small clusters, resembling reticulum cells although they often showed a rounded form with clear cytoplasm, resembling a halo about the nucleus. Granules often could be demonstrated with the periodic acid-Schiff stain in the cytoplasm of these cells. Reticulin fibrils

coursed predominantly around blood vessels and in fibrous septa and were scant in the lymphocytic lobules. Anaplasia was not a feature of our tumors, and invasive tumors could not be separated microscopically from those which were noninvasive.

2. *Thymoma of epithelial type*[15]*:* Sixteen per cent of our tumors were predominantly of this cell type. The epithelial type of thymomas often demonstrated a growth pattern of sheets or cords of epithelial cells with irregular or rounded lobules from variable fibrous trabeculae (Fig. 3, *c*). Peripheral palisading of epithelial cells often was noted around blood vessels, and four tumors showed abundant pseudo-rosette formation. The cells were usually large and polygonal with abundant, slightly eosinophilic cytoplasm, ovoid nuclei, and often with slightly prominent nucleoli. In almost half of these tumors, nuclear size varied slightly. Of particular importance is the fact that this tumor may be easily mistaken for metastatic carcinoma. Except for the epithelial palisade and pseudo-rosette formations (Fig. 3, *d*), true glands were not encountered. The lymphocytic component was usually minimal, and only one of these showed occasional Hassall's corpuscles.

3. *Thymoma of mixed type (reticuloepithelial-lymphocytic):* In 30 per cent of the thymomas examined, the complements of large epithelial cells and interspersed lymphocytes were almost equal (Fig. 4, *a*). This type closely mimics lymphoepithelioma which is a term applied in some classifications of thymomas.[3, 23] This type of thymoma can be distinguished from thymomas with a predominant spindle cell component even though they also may contain an abundant lymphoid background. Microscopically the epithelial component is qualitatively similar to that seen in the thymoma of epithelial type. However, instead of sheets or anastomosing cords, smaller epithelial clusters are seen, particularly along trabeculae, with frequent palisading around small blood vessels. Lobular outlines are usually angular and well maintained; abundant lymphocytes are present, so that one is tempted to think of this as a morphologic stage between the lymphocytic and epithelial types. In the large epithelial cells, which are polygonal in outline, ovoid to round vesicular nuclei and cells with rounded clear cytoplasm are frequently encountered. Anaplasia is not a feature, although one tumor in our group had focal zones of reticuloepithelial cells which mimicked Reed-Sternberg cells because of abundant cytoplasm, binuclearity, and moderately prominent eosinophilic nucleoli. The bulk of the tumor, however, was obviously a thymoma (Fig. 4, *b*).

4. *Thymoma of spindle cell type:* Thymomas of this type made up 24 per cent of the entire group. Microscopically the predominant characteristic is a plump, spindle-shaped cell, apparently derived from the thymic reticuloepithelium (Fig. 4, *c*). This small, dark-staining cell may be mistaken for a lymphocyte on casual examination, but closer scrutiny reveals its tapering cytoplasmic outline and elongated nucleus. These cells occur usually in lobular formations which are richly infiltrated with lymphocytes. The trabeculae dividing these lobules are often thick and composed of cells resembling young

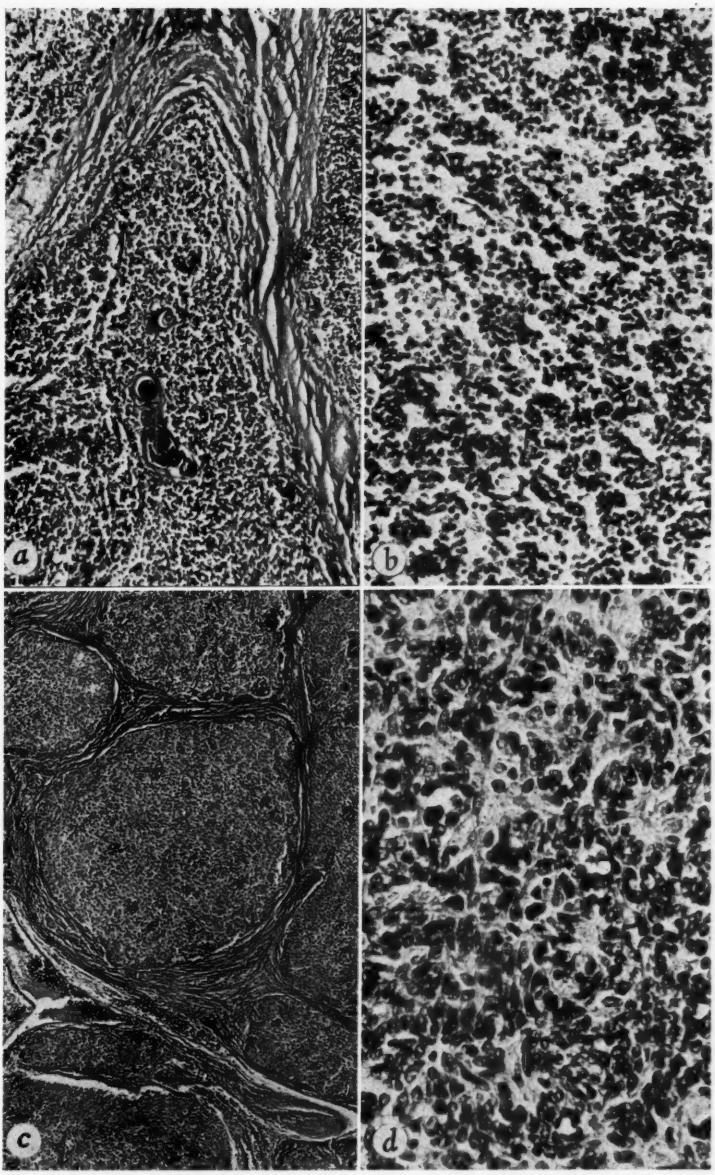


Fig. 3.—Microscopic cell types of thymomas. *a*, Predominantly of lymphocytic type. Lobules of lymphocytes with a few pale epithelial cells and thin trabeculae. Hassall's corpuscles in the center. The patient had myasthenia gravis (×125). *b*, Predominantly lymphocytic type showing many lymphocytes and scattered clear epithelial cells. Same specimen as Fig. 2, *a* (×300). *c*, Predominantly of epithelial type. Large epithelial cells in lobules with rounded outlines separated by fibrous trabeculae. Note sparsity of lymphocytes. The patient had myasthenia gravis (×50). *d*, Predominantly of epithelial type showing pseudo-rosette formation. The patient did not have myasthenia gravis (×360). (Hematoxylin and eosin; reduced 1/10.)

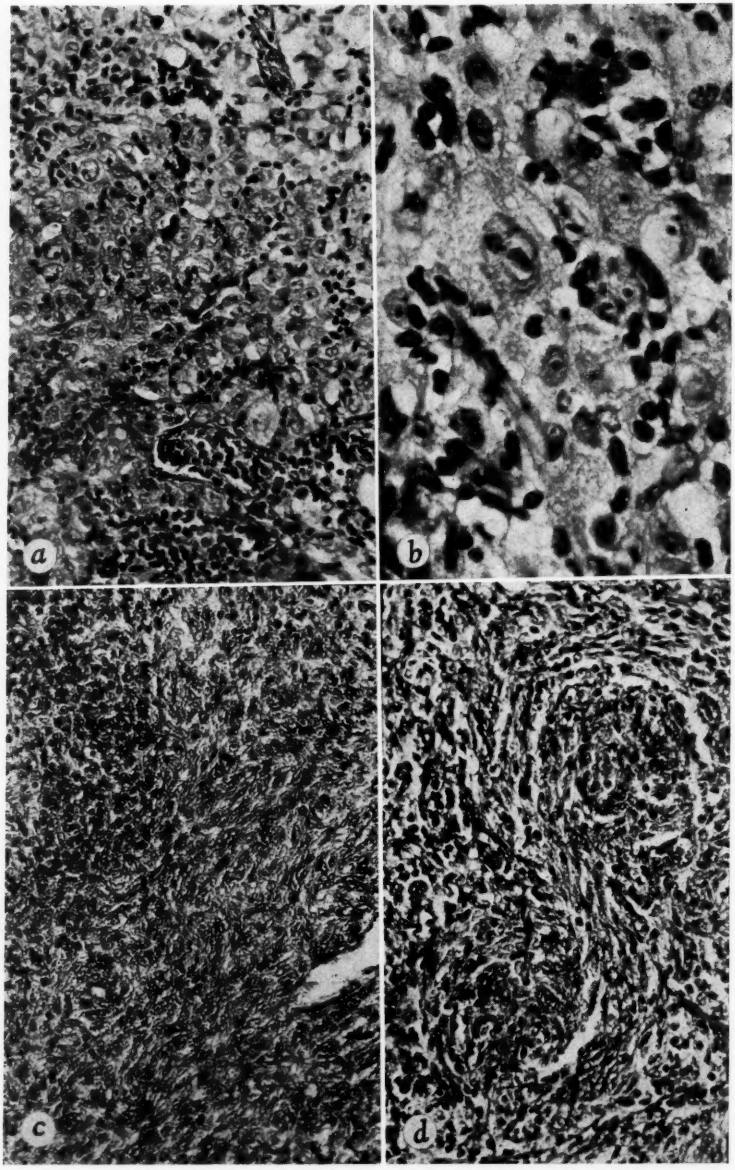


Fig. 4.—Microscopic cell types of thymoma (continued). *a*, Mixed cell type. Mixture of epithelial and lymphocytic cells resembling lympho-epithelioma. The patient had myasthenia gravis. Same specimen as Fig. 2, *e* (×300). *b*, Thymoma of mixed cell type showing macronucleus and prominent nucleoli in an epithelial cell which may be mistaken for a Reed-Sternberg cell. The patient had myasthenia gravis (×650). *c*, Predominantly of spindle cell type. Same specimen as Fig. 2, *b* (×300). *d*, Predominantly of spindle cell type. Whorl formation of spindle cells. The patient did not have myasthenia gravis (×250). (Hematoxylin and eosin; reduced 1/10.)

fibroblasts which show maturation to collagen, but they also may be derived from the reticuloepithelium. Fine reticulin fibrils may be demonstrated between the spindle cells which lie outside of the basement membrane of blood vessels, and may mimic other spindling neoplasms, such as hemangiopericytoma. Zones of multicyst formation lined by these flattened cells may resemble lymphangioma. Whorl formation (Fig. 4, *d*) or crescentic bands of these spindling cells were seen in six tumors, and pseudo-rosette formation, in five. These may represent abortive Hassall's corpuscles or primitive tubular intestinal structures as suggested by Murray[27] for the pseudo-rosette formations. True Hassall's corpuscles were seen in only one tumor. None exhibited nuclear anaplasia.

Other Features and Relationship to Myasthenia Gravis.—Certain other histopathologic features seen in thymomas of the various cell types have been considered in the literature[2, 21, 22, 25] as possibly important in the morphologic identification of cases of myasthenia gravis. Included among these are microscopic cyst formation, perivascular spaces, perivascular lymphocytic cuffing, epithelial palisading, and clear reticuloepithelial cells. These were studied in the present series (Table II).

TABLE II. HISTOPATHOLOGIC FEATURES OF THYMOMAS CORRELATED WITH PRESENCE OR ABSENCE OF MYASTHENIA GRAVIS (138 CASES)

PREDOMINANT CELL TYPE	TOTAL	MYASTHENIA GRAVIS	CYSTS	PERIVASCULAR SPACES	LYMPHOCYTIC CUFFING	EPITHELIAL PALISADING	CLEAR EPITHELIAL CELLS
Lymphocytic	42	Present 20	5	9	12	7	15
		Absent 22	5	1	2	5	15
Epithelial	22	Present 8	3	2	3	2	4
		Absent 14	5	–	2	6	1
Mixed	41	Present 26	8	5	17	21	19
		Absent 15	2	1	6	7	7
Spindle	33	Present 10	5	–	2	2	2
		Absent 23	8	2	–	2	3
Total	138	Present 64	21	16	34	32	40
		Absent 74	20	4	10	20	26

Two main types of cysts occur in thymomas: (1) large cysts and (2) microscopic cysts. The large cyst is usually formed by necrosis or hemorrhage and on microscopic examination shows a fibrous wall often with iron pigment, deposit of fat as cholesterol clefts or foam cells, and calcification. In microscopic cysts, eosinophilic proteinaceous fluid is seen in small lakes within thymoma lobules. Such cysts occurred in about 30 per cent of our thymomas and their incidence in the various cell types of thymomas is shown in Table II. Large cysts with a gelatinous content apparently of similar derivation were seen occasionally. Cysts formed from Hassall's corpuscles were not identified in these thymomas, although a few Hassall's corpuscles or their abortive forms were found in 12 per cent of the entire group. Perivascular spaces around a capillary or venule which usually contained loose stroma or proteinaceous fluid were seen in 15 per cent. In addition, perivascular cuffing of predominant lymphocytes was found in 32 per cent of tumors, either within the perivascular spaces or

merely cuffing small blood vessels. Palisading of epithelial cells around perivascular spaces and blood vessels was noted in 38 per cent, and epithelial cells with clear cytoplasm were seen in 47 per cent. These features were seen in all four subtypes of thymomas and, except possibly for microscopic cyst formation, were more often encountered in thymomas associated with myasthenia gravis than without it (Table II).

Several authors[2, 22, 25] have correlated histopathologic findings in thymomas associated with myasthenia gravis.[2, 21, 25] From our histologic study of these thymic tumors we can agree with Castleman's conclusion that there are no foolproof criteria for differentiating cases of thymoma with and without myasthenia gravis[2] (Tables II and III). Although myasthenia gravis is said to be more commonly associated with thymomas with a large lymphocytic component, it may occur in other cell types as seen in the present study. Features that favor a given thymoma being associated with myasthenia gravis would include (Fig. 5) the presence of perivascular spaces, perivascular lymphocytic cuffing with epithelial palisading, and abundant clear epithelial cells, particularly if the tumor is of a mixed cellular type. In our group, hyperplasia was evidenced by germinal activity in thymus glands removed for thymomas from 9 of 17 patients with myasthenia gravis and in only 2 of 13 patients without myasthenia. Castleman had found hyperplasia of the thymuses removed in 80 per cent of patients with myasthenia gravis without thymoma.

TABLE III. RELATION OF PREDOMINANT CELL TYPES OF THYMOMAS TO MYASTHENIA GRAVIS AND INVASION*

PREDOMINANT CELL TYPE	TUMORS		MYASTHENIA GRAVIS		INVASION	
			ABSENT	PRESENT		
	NO.	PER CENT	PER CENT	PER CENT	NO.	PER CENT
Lymphocytic	42	30	52	48	9	21
Epithelial	22	16	64	36	10	45
Mixed	41	30	37	63	16	39
Spindle	33	24	70	30	5	15
Total	138	100	54	46	40	29

*Based on all surgically resected thymomas or biopsies of thymomas at Mayo Clinic to January, 1961.

Criteria of Malignancy.—Most of the thymomas removed had a capsule of variable thickness and only infrequently did its study give useful evidence concerning invasion. This was due in part to the lobular growth of these tumors which made assessment of invasion difficult and often inconclusive. Intimate incorporation of compressed thymic lobules in the periphery of the tumor also occasionally simulated invasion. When definitive anatomic structures are invaded by the growth, this assessment is more obvious (Figs. 6, *a* and *b*).

In the biopsy of an invasive tumor the finding of fibrous trabeculae may aid in the microscopic recognition of a thymoma which might otherwise be mistaken for a lymphoma or carcinoma. Rounded fibrous nodules are often noted in these tumors which probably represent trabeculae cut transversely.

Definitive criteria of malignancy have been a subject of considerable debate.[28] Some authors have attempted rigid histopathologic distinction between

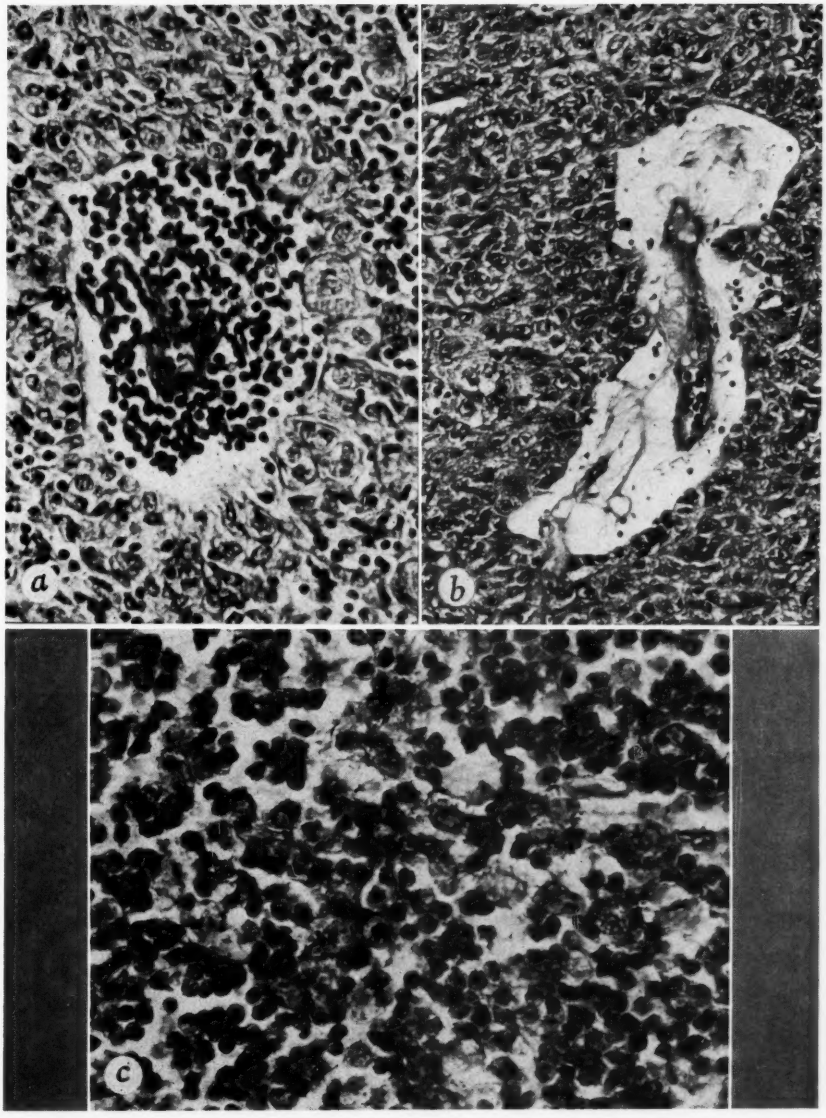


Fig. 5.—Microscopic features correlating with myasthenia gravis. All 3 patients had myasthenia gravis. *a*, Thymoma of mixed cell type showing perivascular lymphocytic cuffing and epithelial palisading. Note clear cytoplasm of epithelial cells (hematoxylin and eosin; ×385). *b*, Thymoma of epithelial type demonstrating perivascular space formation which contains loose areolar tissue, a few lymphocytes and epithelial palisading (hematoxylin and eosin; ×200). *c*, Thymoma of lymphocytic type showing clear epithelial cells within lymphocytic lobules (periodic acid-Schiff; ×600).

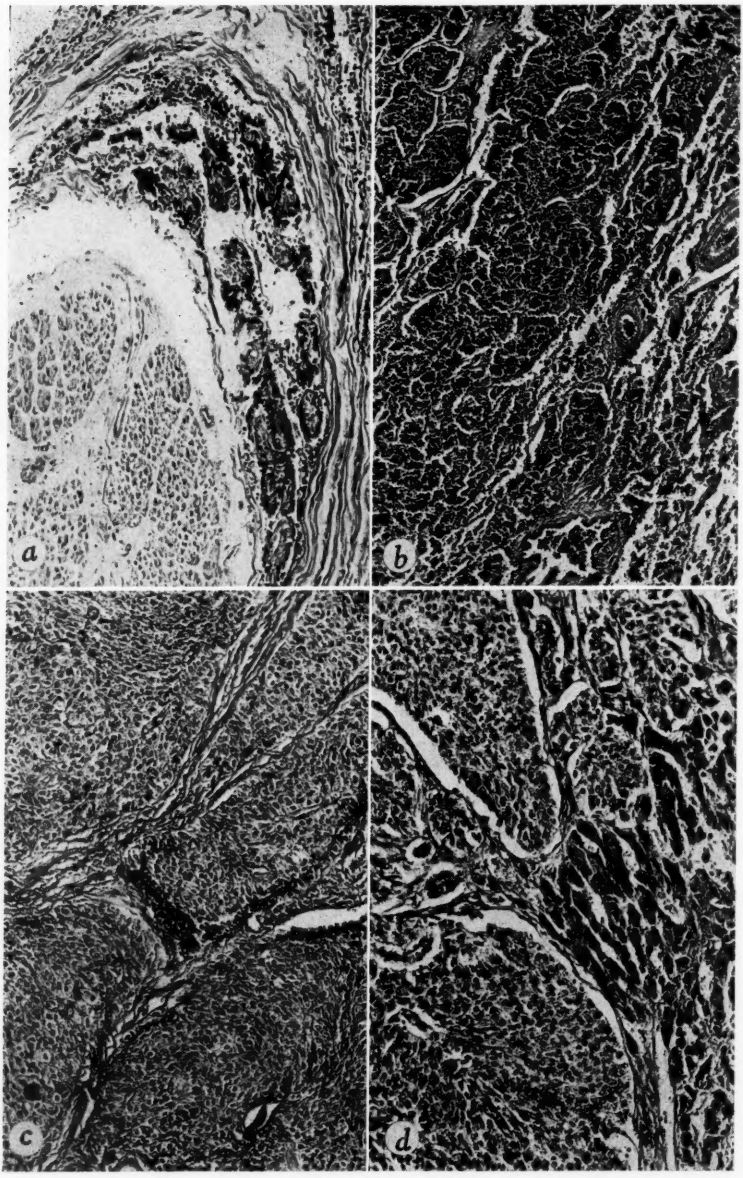


Fig. 6.—Invasive or metastatic thymomas. *a*, Perineural invasion found in capsule of thymoma of mixed cell type (×110). *b*, Invasion of lung by thymoma of mixed cell type. Same specimen as Figs. 2, *e* and 3, *d* (×50). *c*, Metastatic thymoma of epithelial type (specimen from thymus) (×120). *d*, Same case as Fig. 5, *c*. Metastatic thymoma of epithelial type (from liver) (×120). (Hematoxylin and eosin; reduced 1/10.)

what has been termed "adenoma" and carcinoma or lymphoma. Others have called all thymomas "malignant." One is admittedly bewildered by the aggressive invasive behavior of some tumors which are not microscopically distinct from those which are not invasive. Also, obviously malignant tumors in this region make one suspect metastatic or primary malignancy other than in the thymoma. Useful information as to the malignant potential of thymoma is gained by noting its grossly invasive character within the mediastinum, which is usually apparent at operation, and can be further substantiated by selective biopsy with examination of frozen sections. Similar evidence for malignancy is useful in certain other neoplasms, for example, mesothelioma, hemangiopericytoma, and some endocrine tumors. The prognostic importance of the finding of such invasion is shown in Table IV.

TABLE IV. FIVE YEAR SURVIVAL RATES ACCORDING TO INVASION

TUMOR	PATIENTS		LIVED 5 OR MORE YEARS AFTER OPERATION	
	TOTAL	TRACED	NO.	PER CENT*
Invasive	27	26	6	23.1
Noninvasive	64	61	49	80.3

*Inquiry of Jan. 1, 1961. Includes only patients operated on in 1955 or earlier. Hospital deaths are excluded from calculation of survival rates.

That spread may occur also via mesothelial surfaces with implants on the pleura, pericardium, and diaphragm was evident in 6 cases in this series. In one additional case the tumor had invaded structures of the neck; in another retroperitoneal extension had occurred below the diaphragm, and, in 2, metastasis to the liver was seen at necropsy (Fig. 6, *c* and *d*). Metastasis outside the mediastinum is extremely rare from thymoma.

SURGICAL CONSIDERATIONS

The presence or absence of myasthenia gravis is important to the surgeon in the sense that this disease presents far more dangers to the immediate success of the operation than any imposed solely by the thymic tumors. A period of preoperative preparation usually will improve the patient's condition and give the surgeon an accurate idea of the requirements for medication in the early postoperative period when parenteral routes are being employed. Tracheostomy and support of respiratory function by mechanical means contribute much to the improved survival of the ofttimes precariously ill patients. From a technical standpoint the anterior approach through a median sternotomy is the most satisfactory, all-round approach for tumors of the thymus. The occasional diagnostic problem or large tumor projecting to one or the other side can be handled nicely through a posterolateral incision, especially if pulmonary resection is anticipated. Anterior approaches, however, offer the advantage of accurate dissection around the great vessels and into the inferior cervical region and permit adequate resection of the pericardium or even lung, if indicated.

As mentioned before, the surgeon is often in the unique position of being able to evaluate the potential danger of these tumors better from their gross invasive character than the pathologist can on the basis of biopsy alone. But examination of frozen sections of tissue is an inestimable aid to the surgeon in diagnosis and differentiation of adherence or extent of invasion of the neoplasm. The gross characteristic of invasiveness, not simply adherence, is an important prognostic sign as shown in Table IV. The patient with a tumor that lacks invasive qualities has greatly improved chances of living 5 years after operation.

Almost 30 per cent of our 138 patients had invasive growths, and all but one of the six hospital deaths (4.3 per cent) were in these patients. When we also considered the fact that some patients survived several years even with tumors that were not resectable it seems reasonable to limit an aggressive resection if the immediate risks appear to be particularly imposing. Some favorable responses to x-ray therapy support such rationale. We would emphasize, however, that tumors of the thymus, particularly when large, can appear to be very adherent to adjacent structures but still are not invasive. Such tumors are amenable to complete removal.

PROGNOSIS

Sixty-three per cent of our patients survived 5 years or more after operation (Table V) and it was surprising to note that the 5 year survival of patients with myasthenia gravis was approximately the same as that of those without myasthenia (Table VI). The fact that 15 (23 per cent) of the 64 patients with myasthenia gravis had invasive tumors dispels the myth that these patients almost invariably have benign tumors. Approximately 35 per cent of the patients without myasthenia had invasive tumors. Whereas more of this group died as a direct result of the tumor, the ravages of myasthenia gravis claimed a sufficient number of the other group to almost balance the 5 year survival rate. The 10 year survival rate (Table V) is indicative of further mortality from the tumor, and this is more clearly evident when we see individuals who live 5 to 10 years and then die of the effects of the tumor. Of the myasthenic and nonmyasthenic patients with invasive growths, 4 lived 5 or more years after operation, and one of these had biopsy alone. Because these tumors have rarely metastasized to distant critical areas but have killed mainly by local extension to intrathoracic structures, they often have been associated with unexpectedly long survival[29]; in fact, the average survival of 23 patients with tumors that could not be resected was nearly 2 years.

TABLE V. THYMOMA: SURVIVAL RATES

PERIOD (YEAR)	PATIENTS		LIVED BEYOND INDICATED PERIOD	
	TOTAL	TRACED	NO.	PER CENT*
3	107	104	80	76.9
5	91	87	55	63.2
10	48	46	23	50.0

*Based on traced patients. Inquiry of Jan. 1, 1961. The 3 year group includes only patients operated on in 1957 or earlier; the 5 year group, 1955 or earlier; the 10 year group, 1950 or earlier. Hospital deaths are excluded from calculation of survival rates.

TABLE VI. FIVE YEAR SURVIVAL RATE AFTER OPERATION FOR THYMOMA: PATIENTS WITH AND WITHOUT MYASTHENIA GRAVIS

	PATIENTS		LIVED 5 OR MORE YEARS AFTER OPERATION	
	TOTAL	TRACED	NO.	PER CENT*
With myasthenia gravis	47	47	30	63.8
Without myasthenia gravis	44	40	25	62.5
Total	91	87	55	63.2

*Based on traced patients. Inquiry of Jan. 1, 1961. Includes only patients operated on in 1955 or earlier. Hospital deaths are excluded from calculation of survival rates.

Survival was better among patients with thymomas of spindle cell and lymphocytic types than in the other groups (Table VII). As expected, this was related directly to the growth characteristics of tumors of these cell types. Gross encapsulation and good demarcation were evident in a majority of these tumors.

TABLE VII. FIVE YEAR SURVIVAL RATE OF PATIENTS AFTER OPERATION FOR THYMOMA BY PREDOMINANT CELL TYPE

PREDOMINANT CELL TYPE	PATIENTS		LIVED 5 OR MORE YEARS AFTER OPERATION	
	TOTAL	TRACED	NO.	PER CENT*
Lymphocytic	19	18	14	77.8
Epithelial	18	18	8	44.4
Mixed	29	29	16	55.2
Spindle	25	22	17	77.3
Total	91	87	55	63.2

*Based on traced patients. Inquiry of Jan. 1, 1961. Includes only patients operated on in 1955 or earlier. Hospital deaths are excluded from calculation of survival rates.

EFFECT OF X-RAY TREATMENT

At least 39 of the 138 patients received x-ray therapy at one time or another. It was impossible to determine the dosage in most of the cases, but in the majority there was evidence that the total dose was small. Beneficial effect of the x-ray therapy was evidenced in some patients by diminution of shadows in roentgenograms of the thorax. In one patient who had been given x-ray therapy after an inoperable tumor was found at operation, necropsy later revealed no evidence of tumor. Other authors have recorded that thymic tumors have seldom, if ever, disappeared completely with x-ray treatment and if any portion of the tumor did recede it was invariably the lymphocytic component, for such treatment had little or no effect on the epithelial cells.[4, 30] We are not able to say which tumors of the thymus will certainly respond to x-ray therapy, but there is sufficient evidence of beneficial effect in some patients to indicate that intensive x-ray therapy should be given to all patients whose tumors cannot be excised completely.

COMMENT

The various clinical syndromes associated with thymic tumors provide fascinating ramifications for speculation and research. Retrospective studies obviously offer little help in solving these puzzles, and we need to wring from

every patient with thymoma the information that may provide the pieces to the puzzle. We need special studies of the effect of thymectomy on hematopoiesis and on body proteins and their derivatives. Our experiences and those of others[31] have demonstrated the beneficial effect of thymectomy in myasthenia gravis, particularly for young men and women. Investigation of the effect of thymectomy on these and other factors in such patients should be fruitful.

Our review indicates that we may need to reconsider a statement in a previous report that "removal of a thymoma from a patient with myasthenia gravis has no evident influence on the course of the disease."[5] The number of patients does not permit dogmatism, but 28 per cent are doing very well with respect to their myasthenia gravis and tend to dispel the shadow of complete discouragement in these patients with thymoma. We noted, however, at the time of follow-up study that approximately half of the patients with myasthenia gravis and tumor were dead. However, on another tack we find that of patients operated on 5 or more years ago (Table VI), 63.8 per cent lived for 5 years or more. The potential killing powers of both entities involved make this a surprisingly good survival rate.

There have been many objections to the use of the term "thymoma" to designate these tumors. We would be the first to agree that this is not a "simple" tumor, but complicated classifications have added little of practical assistance and, on the basis of our present knowledge, we see no need to alter the term. Correlation of the operative, gross, and histologic findings has resulted in a classification based on certain predominant cell types. These are obviously not rigid and all-inclusive designations. Some merit may be inherent in such a simple subgrouping from a prognostic standpoint and Table VII reveals that tumors that are composed predominantly of lymphocytic or spindle cells had the better prognosis. Tumors of these cell types were more often encapsulated, and lack of invasion (Table IV) is of more prognostic significance than is the cell type.

The designation of thymic tumors as "malignant" has rested on precarious ground owing to the great personal component in the interpretation of gross invasion and simple adherence and the rarity of true anaplasia in these thymic tumors. In fact, when anaplasia is most prominent, the identifying features of thymic tumor disappear. One then must rely on anatomic location for a presumptive identification, but because of the close quarters in the mediastinum which is the source of many tumors, definite conclusions about thymic origin may be questioned. Certainly all anaplastic tumors cannot be excluded by simple definition although we have attempted to limit this group of tumors by the histologic criteria previously outlined.

We recommend an aggressive attitude toward thymic tumors whether or not myasthenia gravis is associated. However, we must point out that although removal or partial removal of a tumor seemed to impose undue risk on the patient, many such patients in our series survived for considerable periods. The activity of thymic tumors is almost exclusively limited to the thorax, and death, when it occurs, usually follows the compromising effects of the growth on cardiorespiratory function.

It is discouraging to look hopefully at the information we have compiled about these patients and realize that there are few statements we can make with finality. We can repeat with assurance a sentence from the report by Effler and McCormack[3] in 1956 that the "intriguing subject of thymic neoplasms still requires new thought and clarification."

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Discussion

DR. WILFORD B. NEPTUNE, Boston, Mass.—The Department of Pathology at the New England Deaconess Hospital has likewise been reviewing the patients with thymoma, and, since most of them constituted our own patients, I would like to show some of the preliminary findings.

These patients have been somewhat selected in that none was operated upon primarily for myasthenia gravis. All patients with lymphoma and, in particular, Hodgkin's disease, have been excluded. The follow-up study has been 100 per cent effective and this particular group has been followed from 2 up to 18 years.

[Slide] In 48 patients with thymomas, selected as mentioned 29 patients had surgical excision only. There has been no recurrence in these patients. In 4 patients who had surgical excision together with x-ray therapy, there has likewise been no evidence of recurrence.

[Slide] In 2 patients, total excision was impossible. One had irradiation and subsequently died of the effects of irradiation alone one year later. One has had no radiation therapy and is alive over 2 years later.

In general, our preliminary conclusions are that from a microscopic standpoint, one cannot determine malignancy or prognosis. Prognosis is based solely on the extent of the lesion at the time of operation. With regard to the patients with lymphoma and Hodgkin's disease, our preliminary findings show that if the lesion is confined to the thymus, and it appears to be a unifocal lesion, the long-term follow-up study is similar to the study of the tumor which can be completely excised.

DR. BERNATZ (Closing).—The activity of these tumors is usually confined within the thorax so these patients die of cardiorespiratory complications if they don't succumb to the associated myasthenia gravis.

However, we have had 2 patients with isolated metastases to the liver not related to contiguous metastases, and not related to ligamentous structures nearby, so that there is no reason to think that these tumors never metastasize to distant organs.

AN ETIOLOGY OF ACUTE RESPIRATORY ACIDOSIS

Richard M. Peters, M.D., Thomas B. Barnett, M.D. (by invitation), and Robert Zeppa, M.D. (by invitation), Chapel Hill, N. C.

ACUTE respiratory acidosis is being recognized more frequently as our concern and knowledge about carbon dioxide retention increase. It is also probable that the incidence of respiratory decompensation has gone up commensurate with an increase in complicated cardiopulmonary surgery.[1] The manifestations of acute respiratory failure are protean—tachypnea and shallow breathing in a patient who is restless may be followed at a later stage by drowsiness, slow respiration, and vascular collapse. The etiology of this shock-like state may be difficult to assess on purely clinical grounds. Knowledge of the total CO_2 concentration in venous blood is not adequate to clarify the picture. Without an accurate arterial blood pH and pCO_2 determination, it is difficult to differentiate certainly metabolic alkalosis and acidosis from respiratory alkalosis and acidosis. In the postoperative or post-traumatic patients there may be a mixed respiratory and metabolic acidosis with a diminished total CO_2, or in patients with chronic respiratory disease the total CO_2 may be elevated to give a partially compensated respiratory acidosis.. The recent improvements in means of measuring pH and total CO_2 may allow us to have these methods as generally available as are means of measuring serum sodium and potassium.

A better understanding of the mechanics of respiration and the manner in which a person responds to respiratory stimuli should clarify the problem encountered in respiratory failure.

Previous work in our laboratory[2] showed that the pressure necessary to inflate the lung increased as the arterial pCO_2 rose in dogs. Since respiratory acidosis is characterized by a rise in arterial pCO_2, studies of the mechanics and work of ventilation during hypercapnia were undertaken. At the same time, we were studying the ventilatory response of dogs with increased respiratory dead space. In both of these groups of experiments the work of breathing is affected and correlation of the findings seemed to afford an explanation for respiratory failure.

It is important to define the parameters of pulmonary mechanics and work. These are: (1) the pressure necessary to maintain the lung at a given volume

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without airflow—the elastic resistance, or the reciprocal of this which is the *compliance of the lung;* (2) the pressure necessary to move air at any given flow rate in or out of the lung and to overcome the friction in movement of tissue, or the *nonelastic resistance;* (3) the work necessary to stretch the lung, *elastic work;* and (4) the work necessary to overcome the resistance to movement of air in or out of the lung and overcome tissue friction, the *nonelastic work.*

Work is defined as the force required to move an object a certain distance, or the product of force times distance. Pressure is force per unit of area, and volume change is a measure of distance per unit of area. Therefore, work can be measured as the product of pressure times change in volume. It is possible to measure these four quantities defined above if we know the pressure across the lung, volume change, and flow rate. The work of breathing is a critical cost which we must pay to get adequate oxygen and eliminate carbon dioxide. The efficiency of this mechanism can be altered in many ways. Clinical examples of these changes are: pulmonary edema, which makes the lungs less compliant and thus more elastic work is necessary to stretch them, and asthma, which narrows the bronchioles and so more nonelastic work is necessary to move air in and out. Loss of elasticity of the lung makes the elastic work less, but the nonelastic work increases to a greater degree. This latter is an important aspect of the total problem of respiratory failure. It must be remembered that the bronchi are not rigid tubes and that pressure applied across these bronchi affect their diameter. For example, if a positive intrapleural pressure is needed for expiration because the elastic recoil of the lung is inadequate, as in emphysema, the airway resistance and work of expiration increase, since the bronchi are being collapsed by the force being used to expel air. Thus, the amount of air moved for any given respiratory exertion in such a patient progressively decreases as the pressure required to accomplish this change in volume increases; or to put it another way, the effort becomes increasingly ineffective in ventilating the lungs. During inspiration at high volumes the lung is hard to stretch, and thus any given unit of ventilation requires added work. Studies by Marshall and his co-workers[3, 4] have shown that we assume a position and depth of respiration which makes the best compromise in terms of efficiency so that added elastic and/or nonelastic work of breathing will result in a minimum of total work for the necessary air exchange.

ANIMAL EXPERIMENTS

In our first group of experiments, which we are reporting in detail elsewhere,[5] the mechanics and work of respiration were studied while animals breathed air and 7.5 to 20 per cent carbon dioxide with 25 per cent oxygen. To measure these ventilatory mechanics, anesthetized dogs with tracheostomy in place and whose chests had been widely opened were ventilated with a specially designed pump. The pump was electronically driven and controlled so that flow rate and volume were constant and these could be continuously recorded on an oscillograph. The pressure at the tracheostomy was also continuously recorded. The volume of gas pumped into and out of the lung was then plotted

against the pressure. Fig. 1 is an actual plot from one experiment while the dog was ventilated with air. The open dots represent such a plot and they enclose a loop (the area depicted by horizontal and slanting lines). The point *A* is where no air flow is occurring as the direction of respiration changes from expiration to inspiration and *C* is where inspiration is changing to expiration. Since there is no flow at these points, all of the pressure exerted acts to maintain the lung at this volume and none to move air. If equilibrium has been reached, the pressure in the alveoli is the same as the pressure at the tracheostomy. The slope of the line connecting these points depicts the *compliance* of the lung.

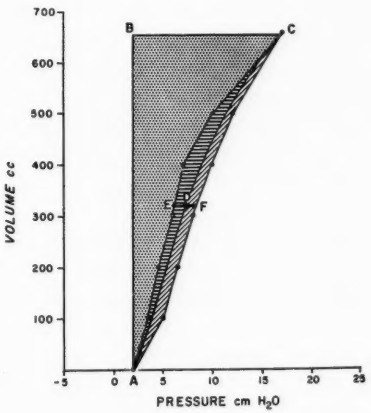

Fig. 1.

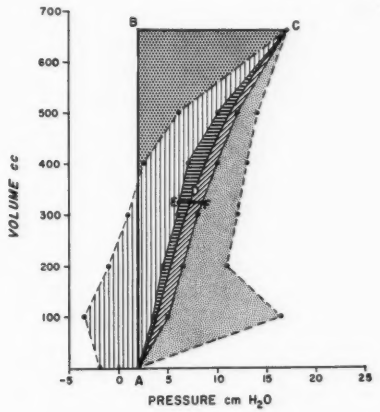

Fig. 2.

Fig. 1.—*Volume-pressure (work) plot – room air.*
Legend: Slope of line *ADC*—compliance. *ED* and *DF*—pressure necessary to overcome nonelastic resistance at any specified volume. Area of *ABCD*—elastic work (dots + horizontal bars). Area of *ADCF*—nonelastic inspiratory work (slanted bars). Area of *AECD*—nonelastic expiratory work (horizontal bars).

Fig. 2.—*Volume-pressure (work) plot – 15 per cent CO_2.* This plot is superimposed on Fig. 1. The increase in work is depicted by the finely stippled and vertically barred areas. Note that nonelastic resistance has increased threefold (*DF* is extended to edge of stippled area).

This line is not straight in this diagram as there was no pause in the pump cycle at *C* and equilibrium was not reached and, therefore, recorded pressure is artificially high at this volume. The difference between the line *ADC* and either limb of the loop at any given volume point, such as *DE*, measures the pressure necessary to move air. Pressure differences to the left of the line *ADC* are those required in expiration and to the right in inspiration. This pressure difference divided by the flow is equal to the nonelastic resistance.

The elastic work is equal to the pressure necessary to stretch the lung multiplied by the volume change. This is equivalent to the sum of the areas depicted by the stippled area and the horizontal lines in Fig. 1, or the area *ABC*. The nonelastic work is equal to the pressure necessary to overcome the flow resistance multiplied by volume change, or for inspiration to the area depicted by slanted lines and for expiration to that depicted by the horizontal lines. The

area representing expiratory nonelastic work is included in the area of elastic work because, at normal rates and depths of breathing, expiration is achieved by the use of potential energy stored during inspiration.

After the control data had been obtained, the test gas was administered to the dogs. Fig. 2 is an illustration of the effect of 15 per cent CO_2 which led to an arterial pCO_2 of 104 mm. Hg in the same dog as depicted in Fig. 1. In this graph we have superimposed the data from the period of carbon dioxide breathing on Fig. 1. The slope of the line *ADC* was essentially unchanged as was the area of the triangle *ABC,* so that the compliance and elastic work were unchanged. In most instances, there was a fall in compliance and an increase in the elastic work of breathing. While these changes were statistically significant, they were quantitatively small. The area of fine stippling represents a marked increase in inspiratory work and the vertical-lined area, representing the increase in nonelastic expiratory work, goes outside the triangle *ABC*. This means the elasticity of the lung was not adequate to expel the air, and the pump had to suck air from the lung. The distance from the line *ADC* to the new loop is tripled, indicating that nonelastic resistance has tripled since flow is the same. Nonelastic work is similarly increased.

Statistical analysis of all the data shows there is a significant increase in nonelastic work and resistance up to two and a half times the control as the pCO_2 rises from 20 to 120 mm. Hg. The elastic work simultaneously increased approximately 15 per cent.

In the second group of experiments reported in detail elsewhere,[6] we were interested in determining the ventilatory response in dogs in which respiratory work had been artificially increased. Dogs prepared with permanent tracheostomies had varying lengths of tubing attached to the tracheostomy to alter the volume of dead space.

With a normal respiratory dead space, they were given 3 to 6 per cent CO_2 to breathe and the alveolar and minute ventilations were measured. Then 300 c.c. of dead space was added and the gases administered again. The minute ventilation was then plotted against arterial pCO_2 (Fig. 3). It is apparent that the minute ventilation is essentially the same for any given arterial pCO_2. The gray lines which represent dogs with added dead space are higher on the graph than the black, as might be expected, but the slope is the same and the points are not statistically different. In Fig. 4 the alveolar ventilation is plotted against arterial pCO_2. In this it is apparent that the gray lines are to the right of the black and are more horizontal. In other words, with increased dead space the alveoli receive less air for any given level of pCO_2, although the minute ventilation is the same. Minute ventilation is a rough measure of respiratory work. These experiments show that the amount of respiratory work performed for any given level of pCO_2 is the same whether or not this gives adequate alveolar ventilation.

A second group of dogs,[7] similarly prepared, had minute and alveolar ventilations and arterial pCO_2 measured before and after adding 500 c.c. of respiratory dead space. Fig. 5 is a plot of the minute ventilation during control

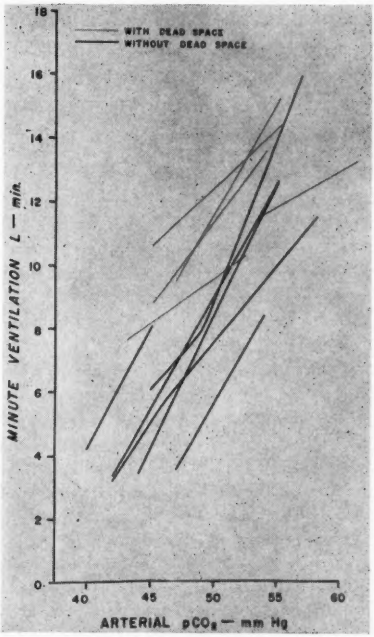

Fig. 3.—*Minute ventilation with and without dead space while animals breathe 3 to 6 per cent CO_2.* Note similarity of response with and without added dead space. Changes in minute ventilation on breathing CO_2 are similar for both groups.

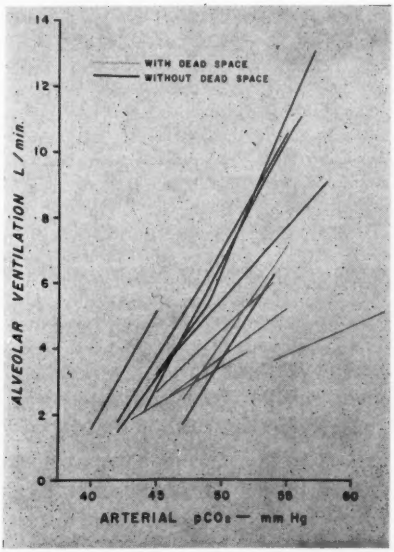

Fig. 4.—*Alveolar ventilation with and without dead space while animals breathe 3 to 6 per cent CO_2.* Higher arterial pCO_2 shows less increase in alveolar ventilation on stimulation with CO_2. Note more horizontal character of plots.

and after adding 500 c.c. of dead space. There is a marked rise in ventilation but, despite this, there is also a significant rise in pCO_2. In Fig. 6, alveolar ventilation is substituted for total ventilation. There is no rise in alveolar ventilation with added dead space. If minute ventilation is again used as a

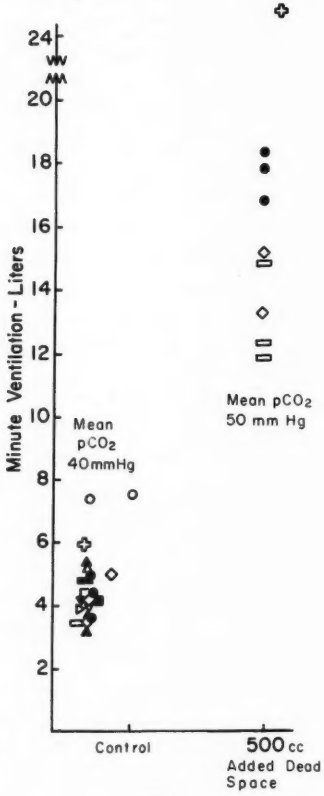

Fig. 5.

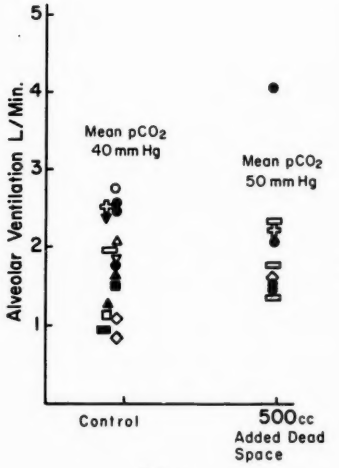

Fig. 6

Fig. 5.—*Minute ventilation before and after addition of dead space.* Note marked rise in minute ventilation with associated rise in pCO_2.

Fig. 6.—*Alveolar ventilation before and after addition of dead space.* Note failure of alveolar ventilation to rise despite 10 mm. Hg rise in pCO_2.

rough estimate of respiratory work, it is apparent that more work is done. The added work produces more CO_2 but, without increased alveolar ventilation, the added CO_2 produced is not eliminated and the arterial pCO_2 rises.

It seems that an increase in pCO_2 elicits a response which calls for a certain number of units of increased work.[8] If this work is effective, it will return the pCO_2 to normal. If some ventilatory abnormality is present which makes the system less efficient, then the work will not be adequate to maintain normal blood gases and a compromise of an elevation in pCO_2 and relatively low alveolar ventilation results.

CLINICAL MATERIAL

With these facts in mind we would like to review our clinical experience with respiratory decompensation. The patients fall into three groups: (1) patients with chest trauma, (2) postoperative patients, and (3) those with chronic respiratory disease, principally emphysema. A complete illustrative case history of one from each group follows:

Trauma.—Patient No. 2-69-10, a 13-year-old white boy, was admitted to North Carolina Memorial Hospital 9½ hours after being struck by a truck while riding his bicycle. He sustained a fracture between the proximal and middle third of the femur, and skin traction had been applied in the treatment of this injury in another hospital. A laceration of the right anterior thigh was sutured. In addition, he had multiple fractures of the left lateral rib cage accompanied by a pneumohemothorax, and there were questionable spleen and kidney injuries. The systolic blood pressure ranged between 80 to 100 mm. Hg.

Physical examination on admission showed an adolescent boy in acute distress, respirations were 35, fast and shallow, blood pressure was 120/85 mm. Hg, and pulse was 170. He had a fracture of the left femur, and severe abrasions on the face, the left lateral chest, and pubis. He was somewhat disoriented.

X-ray examination showed a fracture of the junction of the middle and upper third of the femur, fractures of the fourth through the tenth ribs on the left side, and pneumohemothorax on the same side. An anterior chest tube was inserted and the left leg was placed in balanced skeletal traction. The pulse rate fell to 110 for a short period and respiratory distress diminished. He had received one liter of blood.

Sixteen hours after the accident his condition had worsened; cyanosis and tachypnea had developed as well as a weak pulse at a rate of 170. The temperature was 102° F. and the blood pressure was 140/90 mm. Hg. He appeared apprehensive and had coarse and fine râles throughout both chests. There had been no urine output since the accident. An emergency tracheostomy was done, secretions aspirated, and the patient was ventilated with a piston-type respirator. He was also given Digoxin and 1,500 c.c. more blood. It was estimated that he had lost 1,000 to 1,500 c.c. from the left thigh and over 1,000 c.c. from the left chest. With this therapy, the pulse rate fell to 130, his color improved, and the blood pressure became stable. The 24-hour urine output was 700 c.c.

At this time a holosystolic Grade 4 harsh blowing murmur was noted, heard best at the left margin of the sternum in the third and fourth intercostal spaces. This had not been noted on three previous admissions. Over the course of 3 days, the pulse rate returned to normal. The patient steadily improved during the next 7 days, at which time the respirator was discontinued since the chest wall was stable. The tracheostomy tube was removed on the eleventh day. He had some difficulty with extensor weakness of the left foot; otherwise the recovery was uneventful. Right-heart catheterization on a later admission showed no evidence of shunt. It is believed that he may have a ruptured chorda tendinea of the mitral valve. He is to undergo left-heart catheterization in the near future. There is no chest deformity.

This boy had a severe chest injury with considerable hemorrhage and probably acute cardiac decompensation. He developed respiratory insufficiency which could only be corrected by controlled respiration. This effectively immobilized the chest and, despite multiple rib fractures, there is no deformity.

Postoperative Case.—Patient No. 10-64-85 was a 46-year-old white salesman. The patient was in excellent health until 2 years before admission when he noted onset of fatigue. Three months prior to admission, an upper respiratory tract infection led to night sweats and fever. This progressed to pain in the left chest. He was given antibiotics which brought about some improvement but he had recurrent bouts of pneumonia. Two weeks before admission, x-ray examination of the chest showed atelectasis of the left lower lobe.

Physical examination showed a healthy-looking middle-aged man. The blood pressure was 105/65 mm. Hg, the pulse rate was 88, and respiratory rate was 18 per minute. The left chest showed some lag on inspiration with dullness and decreased breath sounds below the angle of the scapula on the left side. The rest of the physical examination was not remarkable.

X-ray examination revealed atelectasis of the left lower lobe with a normal cardiac silhouette and no increase in anterior-posterior diameter.

Bronchoscopy was done and poorly differentiated squamous cell carcinoma was found just below the orifice of the left upper lobe and bronchus.

At operation, the left lower lobe was completely atelectatic and there were many adhesions to the diaphragm. Pneumonectomy with resection of part of the atrium was necessary because of a tumor thrombus in the inferior pulmonary vein. During operation the patient was difficult to ventilate and the left lung did not collapse. The patient was given 1,500 c.c. of blood during the operation to replace the calculated blood loss. In the immediate postoperative period, he developed hypotension without tachycardia, which did not require any therapy. Postoperative x-ray examination showed no shift of the mediastinum. Eighteen hours after operation the patient developed a sinus tachycardia of 120 to 160 accompanied by a gallop rhythm. The patient was given Digoxin intravenously. During the course of the day there developed progressive slowing of respiration down to 12 a minute, cyanosis, tachycardia, and coma. The arterial pH was 7.19, total CO_2 was 30 mEq. per liter, pCO_2 was 73 mm. Hg.

Tracheostomy was performed and the patient was ventilated with a piston-type respirator. Three hours later the pH level had returned to 7.42, the total CO_2 was 24 mEq. per liter, and pCO_2 had returned to 37 mm. Hg. However, it took 6 hours for the blood pressure to stabilize and the pulse to return to normal. Twenty-two hours after the first use of the respirator it was discontinued. The patient maintained normal blood gas levels and had no further difficulty.

This is a man who probably had hypercapnia during operation and developed progressive respiratory failure postoperatively. Correction interrupted the chain of events and he was able to maintain normal respiratory function after only 24 hours of artificial ventilation.

Chronic Pulmonary Disease.—Patient No. 4-86-01 was a 62-year-old white woman who had been admitted to North Carolina Memorial Hospital ten times in the past 4 years. She had a past history of severe pertussis and influenza, as well as a history of chronic asthma. For the past 5 years the respiratory disability had increased accompanied by the development of cor pulmonale. In the 6 months prior to admission she had had five hospital admissions for acute dyspnea associated with confusion and peripheral edema. The arterial pCO_2 level was up to 70 mm. Hg and above on these admissions. She was treated with corticosteroids, assisted respiration with the Bennett respirator, antibiotics, diuretics, and bronchodilators. This therapy offered some relief for short periods of time. She kept a Bennett respirator at home which she used with some benefit.

On the tenth admission, she was in acute distress, with epigastric pain, nausea, and severe shortness of breath. Prior to entry she had been receiving prednisolone, 10 mg., and digitoxin, 0.1 mg. daily, ephedrine, and amobarbital capsules and had used the Bennett respirator intermittently.

On physical examination, the blood pressure was 105/60 mm. Hg, the temperature was 99.6° F., the pulse rate 120, and the respirations 32 per minute. The neck veins were distended. There was a deformity of the left anterior chest wall due to old osteomyelitis and empyema. The breath sounds were decreased and moist inspiratory râles were heard over the posterior chest. Examination of the heart showed a sinus tachycardia, P_2 greater than A_2, and a Grade 2 systolic murmur at the base. No peripheral edema was present, but the liver was palpated 5 cm. below the costal margin. There was moderate epigastric tenderness.

X-ray examination demonstrated flattening of the left upper thorax secondary to old healed rib fractures as well as slight scoliosis of the thoracic spine. The diaphragms were flattened and the costophrenic angles blunted, but there was no significant increase in the anterior-posterior diameter of the chest. The lung fields showed small nodular and reticular shadows of increased density consistent with moderate pulmonary fibrosis. The oval-shaped heart was normal in transverse diameter but showed prominence of the right-sided chambers and the pulmonary artery shadows associated with cor pulmonale. A gastrointestinal series showed the presence of a duodenal ulcer.

The patient was ventilated with a Bennett respirator for 10 minutes every 4 hours. She grew steadily worse until 3 days after admission when she became markedly cyanotic and responsive only to painful stimuli. When ventilated with the Bennett ventilator, her color improved but she remained unresponsive. The respirations were below 20. The arterial blood pH was 7.13, total CO_2 was 44 mEq. per liter, pCO_2 was 120 mm. Hg. A tracheostomy was performed. She improved temporarily after being placed in a tank respirator. This improvement was not maintained, however, and after further deterioration had occurred, repeat blood gas studies showed the pH down to 7.07, total CO_2 43 mEq. per liter, pCO_2 133 mm. Hg, and oxygen saturation 100 per cent. A piston-type respirator was then used and within 2 hours the pH was 7.34, total CO_2 29 mEq. per liter, and pCO_2 50 mm. Hg, although 24 hours later, after the patient had improved clinically, the pH was 7.40, total CO_2 was 43 mEq. per liter, and pCO_2 62 mm. Hg. The piston respirator was used intermittently. She improved while being ventilated and then slowly developed respiratory acidosis again. She was then continuously ventilated for a period of 2 days until the pH, total CO_2, and pCO_2 were maintained at normal levels. Since then she has been able to ventilate herself adequately without oxygen or assistance.

She was discharged on acetazolamide with tracheostomy tube in place but plugged. The patient did not want it removed. Two months after discharge she has continued to be in good condition, with total CO_2 within normal limits.

This case represents a patient with severe chronic pulmonary disease who had repeated exacerbations of respiratory insufficiency until correction of her hypercapnia had been maintained by artificial ventilation so that total CO_2 was returned to normal. Since such correction she has *maintained* her improvement and is able to undertake activities adequate to look after her needs and get some enjoyment from life.

Table I summarizes the findings in all of our cases. All patients had tachycardia, hypotension and cyanosis. The traumatic and cardiac patients were tachypneic and dyspneic. In the pulmonary resection and chronic lung disease groups, these findings were present early but, in the later stages, slow respirations and somnolence intervened. Thus, the picture was similar to shock, and its failure to respond to the usual therapeutic measures could lead to the erroneous conclusion that irreversible shock had occurred. In the patients with heart disease, pulmonary edema complicated the problem in most instances.

The pCO_2 was highest in the patients with chronic lung disease; in the patients with heart disease or traumatic injuries, it was near normal. However, these latter two groups had mixed acidosis so that the pH was depressed even though pCO_2 was not significantly elevated. All patients had a low oxygen saturation despite oxygen therapy. The primary and associated diseases are self-explanatory. All of the patients who had been in accidents had severe injuries in addition to those to the chest.

TABLE I. PATIENTS ON RESPIRATOR

GROUPS	CLINICAL INDICATIONS	LAB			PRIMARY AND ASSOCIATED CONDITIONS	TIME REQUIRED	RESULTS
		pCO_2	O_2 SAT.*	pH			
A. Trauma 6 patients ages, 13-65 yr.	Paradoxical respirations Cyanosis Hypotension Tachycardia Dyspnea Tachypnea	Slight elevation +	Low +++	Normal to slightly low ±	Fractured clavicle (4) Head injury (3) Other fractures (5) Rib fractures (6)	Usually days to weeks until chest is stable (3 days to 3 wk.)	All patients made excellent recovery with good alignment of rib fractures
B. Surgery I. Pulmonary 4 patients ages, 18-71 yr.	Hypotension Tachycardia Dyspnea Tachypnea or slow respiratory rate Somnolence	High +++	Low +++	Low +++	Bronchiectasis (1) Bronchogenic cancer (2) Tuberculosis (1) Emphysema (2) Arteriosclerotic heart disease (1)	Usually required for hours to days in immediate postop. period	1 survived 2 died on respirator 1 of overwhelming sepsis† 1 of cardiac arrhythmia 1 late death, bronchopleural fistula and coronary artery disease
II. Cardiac 4 patients ages, 10-61 yr.	Pulmonary edema Severe mixed acidosis Hypotension Tachycardia Tachypnea	Normal to slight elevation ±	Low +++	Low +++	Interauricular septal defect (3) Pericarditis (1)	Usually 12 to 24 hours (1 patient with cerebral air embolus required 11 days)	All patients made excellent recovery
C. Chronic pulmonary insufficiency 5 patients ages, 51-71 yr.	Infection Somnolence Hypotension Dyspnea Tachycardia Tachypnea or slow respiratory rate	Very high ++++	Low +++	Very low ++++	Emphysema (5) Fibrosis (5) Cor pulmonale (5) Acute infection (4) Chronic uremia (1)	Continuous therapy until infection is cleared and acid-base balance restored (days to weeks)	4 recovered from acute episode 1 died on respirator in renal failure

*Patients receiving O_2 via nasal catheter.
†Only patient whose respiratory insufficiency not controlled on respirator.

The patients with trauma required the longest period of mechanical ventilation to control the paradoxical respiration which characterizes this group. It must be continued until the chest wall is stable or the function restored enough so that paradoxical respiration does not continue. With this therapy these patients recovered without significant chest deformity.

The postoperative patients and those with heart disease required the shortest periods of artificial ventilation and, in these, the most dramatic results occurred. The acute problem was usually promptly alleviated. As the pH was returned to normal, the blood pressure also returned to normal and the patient appeared well compensated. In the pulmonary resection group only one patient died in respiratory failure. He was a 17-year-old boy who, following a second stage of bilateral resection for bronchiectasis, developed *Aerobacter klebsiella* pneumonia which was resistant to all antibiotics and ultimately led to his death. One patient died of an acute arrhythmia after resection of a tuberculous upper lobe that was performed as an emergency measure to control hemorrhage. He had severe pulmonary fibrosis and emphysema. His respiratory acidosis had been controlled when he developed an apparent cardiac arrest. The late death was in a 70-year-old man who had had a lower lobectomy for carcinoma and developed acute respiratory failure in the first 48 hours after operation. This was relieved with controlled ventilation. He died one month later with a bronchopleural fistula, malnutrition, and coronary artery disease, but had been off the respirator for 2 weeks.

In the group with chronic pulmonary insufficiency, one patient died 18 hours after admission. He had chronic renal failure, shock, coma, and respiratory acidosis on admission. He did not respond to any therapy. Four others made good recovery and are able to get along well. It is important to note that until the patients were ventilated long enough to return the total CO_2 to normal, they tended to slip back into respiratory acidosis. Some are better since this period of correction than they had been for some months prior to their acute difficulty.

DISCUSSION

In each group of cases, as illustrated by the detailed examples, respiratory decompensation occurred. With hyperventilation to control respiration, this was corrected and the patient was able to maintain adequate ventilation on his own when the acute crisis had been overcome. In each instance, the pCO_2 was elevated and had progressively increased over a period of hours. With our present cumbersome method of measuring work of breathing it has not seemed feasible to undertake it in these desperately ill patients. We have evidence, however, that during operation an elevation in pCO_2 is associated with an increase in airway resistance. This is apparently a vagal reflex. All thoracic surgeons have encountered patients whose lungs were extremely difficult to collapse and whom the anesthetist had difficulty ventilating. With vigorous hyperventilation this resistance can be completely overcome. It is interesting to note that Case 2 had just such a problem and in the recovery room developed the typical fall in

blood pressure associated with hypercapnia and then progressively slipped into respiratory failure. This was corrected in 24 hours and led to no further difficulty. A reasonable explanation is that the hypercapnia and surgical procedure caused an increase in the work of breathing, and the elevation of pCO_2 did not elicit an adequate ventilatory response, so that progressive respiratory decompensation ensued. Correction of hypercapnia and recovery from the associated metabolic acidosis induced by anoxia, restored normal homeostasis, and 24 hours later the patient was able to get along without any respiratory assistance.

The patients with chronic pulmonary disease were harder to get to the point of compensation, but, after artificial ventilation was continued long enough to restore total CO_2 to normal levels, they were in a better clinical state than they had been for months. We are pursuing at present the question of which combination of alterations in total CO_2, pH, and pCO_2 are responsible for the change in nonelastic work of breathing and perhaps for the change in the respiratory control system in these abnormal states.

One of the effects of chest trauma is to alter the work of breathing. A patient with multiple rib fractures can get along quite well immediately following trauma if pneumothorax is controlled. However, as the hours pass and the secretions accumulate in the tracheobronchial tree and edema increases and hematomas enlarge, these patients steadily deteriorate. This picture is described as traumatic wet lung. If the secretions are removed and the chest wall stabilized, such patients are markedly improved.[9] Again, we have a situation in which there is a progressive increase in the amount of effort needed to achieve a given alveolar ventilation and, when this is not achieved, pCO_2 rises, work increases, and this leads to a vicious cycle. The point has been made that this train of events must be prevented because correction is often difficult if not impossible.

The role of metabolic acidosis in altering respiratory mechanics is being investigated at this time. The effects of elevation in pCO_2 on the airway resistance could be due to a fall in pH just as well as to a rise in pCO_2. If so, a rise in airway resistance in metabolic acidosis would be expected. Even if such a rise in airway resistance does not occur, hyperventilation necessary to lower the pCO_2 in metabolic acidosis involves increased work and rarely leads to complete compensation in terms of return of pH to normal. If some injury to the lungs is superimposed on this acidosis, then we may have a logical explanation for the all too frequent occurrence of respiratory acidosis after open-heart surgery.

Thus, in all of these circumstances, we have a situation in which the alterations in acid-base balance apparently contributed to an increase in the work required to get an adequate amount of alveolar ventilation. At the same time the response elicited is in terms of units of work, not alveolar ventilation. Thus, a vicious cycle is set up which can only be reversed by assisting respiration (Fig. 7).

Teleologically at first glance these two phenomena seem to be completely illogical evolutionary developments. On further analysis the purpose is not so ill conceived. The work of Young, Sealy, and others[10, 11] has demonstrated the danger of acute reversal of respiratory acidosis, which can lead to acute cardiac arrhythmias and arrest, probably associated with hyperkalemia. If the airway resistance is increased with hypercapnia, then the correction will be slowed and the hazard of acute cardiac arrhythmia reduced. This potential hazard of acute correction of respiratory acidosis must not be neglected.

A stimulus response regulation based on work rather than alveolar ventilation is perhaps more logical.[12] As respiratory effort is increased, the efficiency of the system decreases. If ventilatory control mechanisms were such as to maintain

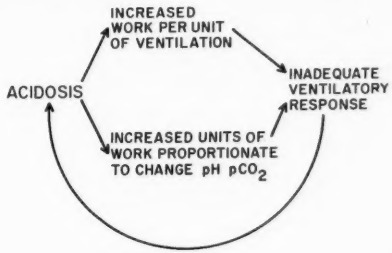

Fig. 7.

normal alveolar ventilation, regardless of the work required, then it can be shown that the oxygen consumed and the CO_2 produced to perform the necessary work could exceed the ability to acquire and eliminate these gases. By regulating the ventilatory response in work units by a feedback system, a response is achieved which arrives at the most efficient compromise.

One of the earliest means of treating these types of respiratory failure was with a tracheostomy. This in itself decreases the work necessary to achieve a given level of alveolar ventilation. Its beneficial effects are probably due, in part at least, to the increase in the alveolar ventilation for each unit of work. Unfortunately, the circumstances in which tracheostomy alone will correct these deficiencies are few. It is, therefore, necessary to resort to some type of mechanical means of ventilating the patient to do the necessary work. The evidence we have presented supports the fact that it is important to return the pCO_2 to normal and to return the respiratory work to normal.

A word is in order about respirators and means of ventilating these patients. We believe the respirator should be simple, compact, and easily maintained and have a good humidifier and bacterial filter. It should be so designed that up to 50 to 60 per cent oxygen, but no higher concentrations, can be given, and decontamination should be simple and effective. Volume regulation without a cuffed tracheotomy tube is superior to pressure regulation.[13] The tight tube requires pressure on the trachea and, if any mishap occurs, the pump could create a dangerously high pressure in the chest. With a volume regulated respirator that permits a large leak around the tracheostomy tube, hypoven-

tilation is the only risk in malfunction. This is not as acutely dangerous as a marked increase in intrathoracic pressure would be. The leaking system has the additional advantage that the patient can learn to talk during the inspiratory cycle, and dead space is made minimal because of the continuous washout. Finally, upper airway secretions are blown back into the mouth where they can be swallowed or removed by suction.

Oxygen concentrations above 50 to 60 per cent are dangerous for two reasons: (1) the undefined toxic effect of 100 per cent oxygen, and (2) the higher concentrations of oxygen wash out the nitrogen, and, if a portion of the lungs is blocked off for only a short period of time, complete collapse can occur as the oxygen is quickly absorbed. In an animal which has had all of the nitrogen washed from its alveoli, occlusion of a bronchus collapses the lung in a matter of 1 to 2 minutes.

A respirator which is triggered by the patient's own respiratory efforts is not satisfactory. It prevents true controlled respiration, which is necessary so that the patient can rest. In traumatic chest injuries, immobility of the chest is absolutely dependent on eliminating the patient's respiratory efforts. Likewise, a pressure regulated respirator with simple controls lacks the precision needed, and the more complicated ones required too much specialized training and maintenance to be generally useful.

No respirators meet all of these requirements. We have found the Morch respirator* satisfies some of the most important of these criteria and could be made to meet them all. It is compact, simple to operate, and relatively foolproof. However, the presently available humidifier is ineffective and no bacterial filter is supplied for a respirator that picks up its air from the floor level. It is difficult to decontaminate but can be sterilized in an ethylene oxide gas sterilizer. This has led to difficulty with the piston cylinder arrangement in that corrosion between the aluminum piston and the brass cylinder leads to jamming of the piston. Siliconizing of these seems to improve this problem. Dismantling the pump to clean the cylinder does not require great mechanical skill but is very time consuming. At present we are informed that these deficiencies are being appraised and design changes worked on to make the requisite improvements.

SUMMARY

We have presented experimental evidence that respiratory failure is related to increase in work of breathing associated with hypercapnia and an inadequate respiratory response to the hypercapnia. These experimental findings have been correlated with our clinical experience.

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DISCUSSION

DR. GEORGE H. A. CLOWES, Cleveland, Ohio.—Dr. Peters was kind enough to let me look at his paper before this meeting and I assure you that he was unable to give you the full story. What he said is really of great importance to all of us. We have recently presented evidence at another meeting showing the great difference that does exist between metabolic acidosis and respiratory acidosis.

It is not just a hydrogen ion concentration shift that does damage to people. A patient whose arterial pH has fallen to 7 because of CO_2 retention from a circulatory disturbance is in far less trouble than a person whose pH has fallen to 7.25 because of lack of oxygen. This is obviously a different situation. As Dr. Peters has said, we can break the vicious cycle of increasing carbon dioxide tension that ultimately leads to circulatory and to central nervous system depression. By increasing the respiratory inflation for a time, a patient may become compensated as to CO_2 elimination. What is more remarkable is that the compensation may be maintained, even in a severely emphysematous individual.

I don't understand why there is a change in the resistance and compliance of the lung. I have wondered whether the carbon dioxide in its own right tends to put up the venous return and cause pulmonary congestion when it reaches this state—I don't have the explanation, but I do understand his dead space experiment. I have used this maneuver to get around the same difficulty in a postoperative cardiac patient who has been allowed to get into a state of hypercapnia due to inadequate breathing as he was recovering. Sometimes we fail to realize that these patients' lungs are sufficiently damaged so that they are unable to compensate for themselves after we have operated upon the heart of the individual. An early tracheostomy and a Bennett respirator, or whatever type we care to use, may be the lifesaving agent.

DR. WILL C. SEALY, Durham, N. C.—It has been my impression for some time that postoperative respiratory acidosis is a much more common complication in thoracic surgery than is generally appreciated. It is a great imitator. It has been confused with coronary artery disease, central nervous system dysfunction, and surgical shock.

The perspiring patient with a low blood pressure may resemble the patient with hypovolemic shock. The mental confusion and sometimes very bizarre neurologic changes may even suggest a cerebral vascular accident. In addition, the added effects of operation, anesthesia, and sedation all confuse the issue. The diagnosis can be made quite readily by doing blood gas analysis.

I have been impressed by the element of bronchospasm that is seen in many patients with respiratory acidosis, even though the patient may not have an asthmatic history. Because of the poor ventilation in some patients, the physical signs of bronchospasm may be very difficult to elicit.

Because of the bronchospasm, we have elected to use, in addition to the methods that Dr. Peters discussed, large doses of steroids—and what do we mean by a large dose of steroid? It is enough to relieve the bronchospasm in a few minutes. This may take approximately 400 mg. This is followed by a drip of 200 to 400 mg. over the next 12 hours. The patient remains on large doses until he has recovered. This, we believe, has been lifesaving. It reduces the secretions resulting from inflammatory reaction in the bronchi and lung parenchyma from the anesthesia and from instrumentation.

These drugs have been successful when atropine, bronchial dilators, and, even, hyperventilation have not been effective.

The success in treatment in the postoperative period has suggested that steroids might be useful in the prevention of this complication. Thus, in more than 100 patients we have preferred to proceed in this way, and have used it in emphysematous patients, patients with asthma, the ones with poor pulmonary reserve, and the debilitated patients. These patients are given the equivalent of about 200 mg. of cortisone acetate 12 hours before operation or, if the patient is asthmatic, until the bronchospasm disappears. This is continued for 5 to 7 days after operation and then gradually decreased.

When it is used in this way, there is no trouble with wound healing, control of infection, or electrolyte imbalance. We use gastric suction until the patient is able to take fluids by mouth.

The fact is that this may be a lifesaving measure in certain patients who have a disseminated bronchial pneumonia in that it may relieve the edema and increase breathing capacity until the antibiotic can be effective. This study of Dr. Peters will certainly make all of us more aware of this very important postoperative complication.

DR. JOHN J. CINCOTTI, Albany, N. Y.—Several problems are common to the study Dr. Peters has presented and to our continuing investigation into the methods of postoperative nasotracheal suction. How does one avoid causing an increase in the work of ventilation; second, when is hyperventilation indicated and by what techniques is it attained?

We must be constantly reminded of the physiologic defect inherent in established therapeutic methods. Nasotracheal suction, as popularized by Dr. Haight many years ago, is ordinarily utilized only for the removal of secretions and frequently a punitive motive is appended; it helps the patient respond maximally to our request that he rid himself of retained secretions—"If you do not raise sputum, I'll have to repeat this." Although it does aid the removal of secretion, if nasotracheal suction is continued into the *inspiratory phase* of the respiratory cycle, the work of ventilation increases (unpublished observations of P. O. Anderson and J. J. Cincotti). Additionally, the tidal volume is markedly decreased.

By the simple expediency of permitting nasotracheal suction only during the *expiratory phase* of the cycle, the tidal volume increases, and the functional residual capacity decreases, as the mid-position is lowered. We have observed that a pCo_2 of 70 mm. Hg falls readily toward the normal range, and that a pO_2 of 70 mm. Hg may rise to 120 immediately following this form of hyperventilation during nasotracheal suctioning (unpublished observations of A. A. Siebens and J. J. Cincotti). Thus, we assist ventilation during a procedure which ordinarily exchanges a concomitant desaturation for the necessary gain, that is, removal of secretions in patients unable to do so on their own.

This slide depicts one of the basic studies of the mechanics of nastracheal suction (Boba et al., J. Lab. & Clin. Med. 53: 680, 1959). In the first strip you see that as long as the laryngeal cords are removed from their obstructing possibilities (by a large-bore endotracheal tube) and as long as the tip of the aspirating catheter is in the distal trachea (not captured within the distal bronchial system), then if such a patient is made apneic, the rate and extent of desaturation is primarily a function of the duration of the apnea. This fall in arterial oxygen saturation is not significantly altered by the application of suction,

via the aspirating catheter, throughout the period of apnea. Under these circumstances, the aspirated air is drawn in through the large-bore endotracheal tube and sucked out along with secretions, via the smaller lumened suction catheter. This we have termed "U-flow."

The most important deficit in the postoperative period is encountered when eventually the tip of the sucking catheter occludes, or is captured by, the more distal tree. In this instance, I feel that a catheter that incorporates the principle of U-flow will prevent worsening of the postoperative pulmonary A-V shunting mechanisms, should they exist.

DR. PETERS (Closing).—Dr. Sealy and I have discussed the problem of postoperative steroid therapy which he has used so successfully. It may well be that steroids prevent the bronchial constriction we have shown here by prevention of histamine release or by cutting down secretions. The control of secretions would prevent increased work of breathing which could lead to the vicious cycle described. Dr. Cincotti's remarks were very interesting, and certainly acute acidosis could be induced if suction is too prolonged. Dr. Clowes is better able to discuss the different systemic disturbances induced by metabolic or respiratory acidosis than I am. In the postoperative or post-traumatic patient a mixed acidosis is likely to occur. A patient who has had a thoracotomy or open-heart procedure may have suffered damage to his lungs. This can increase the work for a unit of ventilation and lead to the vicious cycle mentioned.

Finally, let me state that even in normal subjects there is a point at which the respiratory response leads to a relative decompensation. Roger Bannister, physiologist as well as a great runner, has demonstrated that when he has run to exhaustion, his response to oxygen is very similar to that seen in respiratory acidosis. These limitations of response, as shown by Reilly, are protective. Without the limitations we could reach a point at which more oxygen is utilized and carbon dioxide is produced than could be provided by the increased ventilation. By studying the response of the normal to physical stress we may come nearer to knowing what the physiology of the postoperative period is than by studying the unstressed individual.

BLOOD CHEMICAL CHANGES IN PERFUSION HYPOTHERMIA FOR CARDIAC SURGERY

John J. Osborn, M.D. (by invitation), Frank Gerbode, M.D., J. Bruce Johnston, F.R.C.S. (by invitation), J. Keith Ross, F.R.C.S. (by invitation), Takeshi Ogata, M.D. (by invitation), and William J. Kerth, M.D. (by invitation), San Francisco, Calif.

IT WOULD be redundant to review the advantages of hypothermia to the cardiac surgeon. In our experience, with improved techniques of extracorporeal circulation, the addition of hypothermia, by blood-cooling to perfusion, has added a large measure of safety and reliability, particularly when operation is long and difficult, as in the anatomic correction of tetralogy of Fallot.

In this paper, we will present data accumulated during perfusion with hypothermia induced by blood-cooling in 350 patients undergoing cardiac surgery.

All biologic reactions change with temperature, the most predictable one tending to be a direct relation between speed of reaction and temperature. But, in the search for safer ways of using the advantages of hypothermia, it seems sensible to investigate the chemical systems which show the most obvious sensitivity to temperature change. The blood gases and their transport systems seem especially important to study because the solubility of any gas is inversely related to temperature so that changes in solvent temperature must necessarily affect any chemical equilibria dependent on gas partial pressure. For this reason, our attention has largely been given to carbon dioxide and oxygen and their transport, although changes in potassium, sodium, and extracellular water have sometimes been followed.

MATERIALS AND METHODS

The observations on which this paper is based were carried out during perfusion for cardiac repair in the Cardiovascular Unit, first at Stanford University Hospitals, San Francisco, and, subsequently, at Presbyterian Medical Center, San Francisco. Carbon dioxide concentration in the gas phase was

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measured with a Liston-Becker (Spinco-Beckman) infrared gas analyzer. Blood pH was measured at a temperature of 24° C. with a Beckman Zeromatic pH meter and was corrected to the original blood temperature by a factor of 0.015 per degree C.[1] Oxygen uptake was calculated from the measured blood flow through the machine with intermittent sampling of arterial and venous blood from the machine, the samples being read for oxygen saturation with a Waters Cuvette oximeter, using an assumed oxygen capacity of 20 vol. %. This does not create a large error, as the measurements were usually made on pooled donor-and-patient blood, so that variations in hematocrit were not large. Carbon dioxide elimination or absorption by patients was easily measured directly in the artificial lung, because at all times a gas of known concentration of carbon dioxide was introduced into one end of the lung at a known rate. The gas emitting from the other end of the lung was then continuously sampled, any change in concentration reflected a direct gain or loss of CO_2 in the artificial lung.

The pump oxygenator was, in most cases, the heat-exchanging large disc oxygenator which we have described.[2, 3, 4]

EXPERIMENTAL FINDINGS

In our early work with perfusion at normothermia for open-heart surgery, we used a gas mixture of 5 to 6 per cent CO_2 in the oxygenator. When, encouraged by the early reports of Brown and Sealy and others,[5] we began to explore moderate perfusion-induced hypothermia, we tended to maintain the same rather high CO_2 concentration. This was partly because experimental work in immersion hypothermia by ourselves,[6] Lewis,[7] and Edmark[8] suggested that a high pCO_2 and some acidosis might be desirable during hypothermia. In any case, the high CO_2 concentration of our oxygenator gas lead to the following rather surprising findings which might not have been apparent had we used lower concentrations of carbon dioxide.

HYPOTHERMIA AT HIGH pCO_2

Our first measurements were of the arterial and venous blood pH during cooling and warming. In the following discussion, arterial blood refers to blood leaving the artificial lung and venous blood to that leaving the patient and entering the artificial lung. "Blood temperature" or "patient temperature" refers to the temperature of the mixed venous blood leaving the patient, unless otherwise stated. Careful measurements, corrected for temperature of the blood at the time of sampling, showed a pronounced narrowing of the normal difference in pH between arterial and venous blood during cooling and widening of the difference during rewarming. The most obvious explanation of a diminished arteriovenous pH difference would be a diminished output of carbon dioxide by the patient.

Carbon dioxide excretion was, therefore, measured directly in the gas phase, by sampling with an infrared analyzer at the "expiratory end" of the artificial

lung. As experience was gained with progressively deeper hypothermia to a temperature of 16° C., it was found, if the artificial lung was ventilated with gas containing CO_2 in a concentration of 5 per cent or more, the patient's own CO_2 output was not only reduced during cooling but, that, during rapid cooling, carbon dioxide was absorbed in large quantities by the patient. However, when a constant temperature was maintained for 30 minutes or more, CO_2 absorption

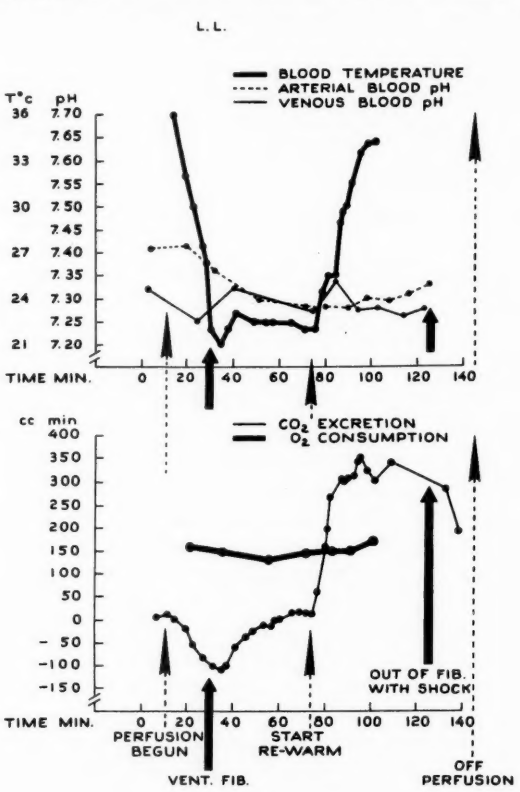

Fig. 1.

gradually ceased and most patients gradually began to eliminate carbon dioxide again at a reduced rate in proportion to their temperature at that time. On rewarming, all patients rapidly increased their carbon dioxide output, finally putting out CO_2 almost explosively, at rates very much higher than normal. During this rewarming, the mixed venous pCO_2 sometimes rose to extraordinary heights, often as high as 85 mm. Hg, and the volume of CO_2 eliminated sometimes reached 500 c.c. per minute in individual patients. Fig. 1 presents data on a typical patient cooled to 21° C.

The solubility of any gas is inversely proportional to the temperature of the solvent, so it should not be surprising that a larger amount of carbon dioxide

should dissolve in cold blood (at a fixed pCO_2) than in warm blood. Yet, simple calculations on the solubility of carbon dioxide in water at different temperatures showed that our patients actually absorbed approximately twice as much CO_2 per degree temperature drop as could be accounted for by increased solubility alone. The blood buffering system must, therefore, participate in this absorption.

If a large volume of CO_2 is absorbed during cooling and then must be eliminated during rewarming, it is obvious that this must load the transport mechanisms of the circulation and lungs. We found, by experience, that extracorporeal circulation and oxygenation should be maintained in these patients during rewarming not only until a temperature near normal was reached, but also until the rapid rise in venous pCO_2 was over, in other words, until the greater part of the extra absorbed CO_2 had been eliminated. Even so, we sometimes found a later carbon dioxide retention, lasting hours, which could be due either to inadequate circulation or inadequate ventilation or both. Although it did not appear to handicap patients who had adequate blood pressure and lung function, it may well have been a significant added load on patients who for one reason or another had circulatory or pulmonary difficulties postoperatively.

One may then properly ask "if patients cooled on high CO_2 concentrations absorb it during cooling and then have to blow off an extra load of CO_2 during rewarming and in the next few hours, why not reduce the concentration of CO_2 in the oxygenator gas and hence make less or none available to the patient other than his own metabolic CO_2?" In an attempt to answer this question, a series of patients were cooled using lower concentrations of CO_2 in the oxygenator.

HYPOTHERMIA AT pCO_2 UNDER 30 MM. (4 PER CENT)

Thirty patients were cooled to temperatures under 25° C. using 4 to 3 per cent CO_2 in the oxygenator. None of these patients actively absorbed CO_2 during rapid cooling. However, the excretion of CO_2 by the patient still dropped sharply, often almost to zero, for a short time during the most rapid cooling. During rewarming, the pronounced "CO_2 blowoff" which we had noted previously was less striking, although rewarming was still always associated with a rise of mixed venous CO_2 to well above normal and a rise in absolute volume of CO_2 excreted to levels well above normal. Fig. 2 presents data on a typical patient in this series.

In this group of patients, we had the strong clinical impression that we were having more difficulty in reversing ventricular fibrillation during the rewarming phase than we had previously experienced. We noted for instance (Table III) that of 23 patients cooled to below 25°, using 6 per cent CO_2 or more, 30 per cent had reverted spontaneously from ventricular fibrillation during rewarming, but, in 21 patients cooled with oxygenator pCO_2 under 4 per cent, only 3, or 14 per cent, spontaneously reverted and several required repeated electrical defibrillation to a degree which we had not experienced before.

HYPOTHERMIA WITH ACIDOSIS INDUCED BY HCl (EDMARK TECHNIQUE)

It was suggested by Edmark[8] that acidosis produced by intravenous administration of hydrochloric acid may be beneficial during hypothermia. This seemed in accord with our observations above, although the acidosis had been produced in our patients by relatively high pCO_2. However, the Edmark technique has one important advantage, that is, the acidosis produced during cooling by addition of HCl can be rapidly neutralized during rewarming by intravenous addition of an equivalent amount of $NaHCO_3$ without loading the circulation with a large amount of excess CO_2 to be excreted. The products of the neutralization are NaCl and H_2CO_3, but in relatively small amounts, the total amount of reagents used in our experience not exceeding 80 mEq. of each. The CO_2 thus liberated could not exceed 2 liters. For these reasons, the next series of 30 patients, cooled to below 25° C., received hydrochloric acid intravenously according to the Edmark technique.* The amount of acid varied, never being over a total of 65 mEq. per patient in adults and proportionally less in children. The drop in pH thus produced was not striking, averaging 0.11 pH unit. Yet, of these patients, 70 per cent defibrillated spontaneously on rewarming and our clinical impression was that these patients awoke in better condition than those in the previous series.

A metabolic acidosis increasing gradually during perfusion has been reported by many workers. We did not find any consistent development of metabolic acidosis in our patients, whether normothermic or acidotic. A convenient rapid way to separate metabolic from respiratory acidosis is by comparing the direct pH of a blood sample with the pH of the same blood after equilibration with gas of known pCO_2. This has been worked out very elegantly by Astrup and his co-workers.[9] The pH of the equilibrated sample essentially is a measure of standard bicarbonate. We have somewhat simplified this technique for operating room use as follows: at regular intervals, a mixed venous sample of blood is drawn and the pH measured, with temperature correction. A portion of the same blood sample is equilibrated in a small tonometer with CO_2 in oxygen with a pCO_2 of 42 mm. It is obvious that any change in pH of the second (equilibrated) sample must reflect a change in metabolic components of acid-base balance, since the pCO_2 is fixed in the tonometer. Detailed derivation of the chemistry will be found in the papers by Astrup[9] and Pierce.[10] The pH of the equilibrated sample can be used to calculate standard bicarbonate by reference to the appropriate nomogram of Astrup or Van Slyke but, as this requires some assumptions, we have chosen to report the pH data directly as read. Approximately 50 patients have been studied during perfusion with this technique, with varying degrees of hypothermia.

*This technique, as used by us, consists essentially of the following: (1) Add 15 c.c. of concentrated HCl to 500 c.c. of 5 per cent dextrose in water. This mixture yields 308 mEq. per liter of HCl. (2) Use up to 250 c.c. or 75 mEq. during cooling. The addition should be made to the venous side of the oxygenator while blood is flowing rapidly to avoid hemolysis. (3) Lower the pH to approximately 7.2. (4) Neutralize with the same milliequivalent of $NaHCO_3$ while rewarming. (5) Correct all pH readings for blood-electrode temperature difference with the Rosenthal factor 0.015 pH unit per degree centigrade.

Figs. 3, 4, and 5 present data for 3 patients undergoing fairly long perfusions, each lasting about 3 hours. The temperature was lowered to below 20° C. in 2 and to 23° C. in the third. Each patient received between 40 and 80 mEq. of HCl intravenously during cooling and an equivalent amount of $NaHCO_3$ during rewarming. In each chart, the dotted line represents the pH of blood at 42 mm. pCO_2. In each case there is a sharp drop at the beginning of perfusion, representing the induced acidosis of the HCl addition. Thereafter, there is no important change over as long as 100 minutes of perfusion. On rewarming,

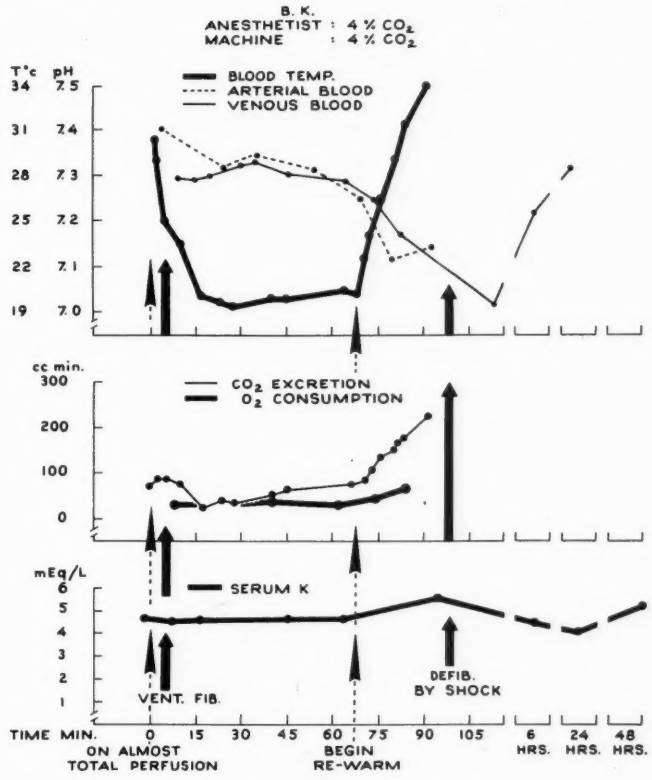

Fig. 2.

there is an abrupt shift back to the original value, which represents the neutralization by the added sodium bicarbonate. The return to the original value is almost always exact, if the bicarbonate is given in equal milliequivalent to the HCl. The third case includes a period of intermittent perfusion at normal temperature, while additional surgery was finished.

Although, as above, we have not found metabolic acidosis developing in patients adequately perfused, it develops very rapidly in patients when the perfusion is inadequate as it does in any patient in shock. In our patients, a

perfusion flow insufficient to raise the mean blood pressure to 80 mm. Hg, or above, has usually been associated with the development of metabolic acidosis. Metabolic acidosis has rarely been detected during perfusion when the blood pressure has been held over 95 mm. Hg mean. It is interesting to note that,

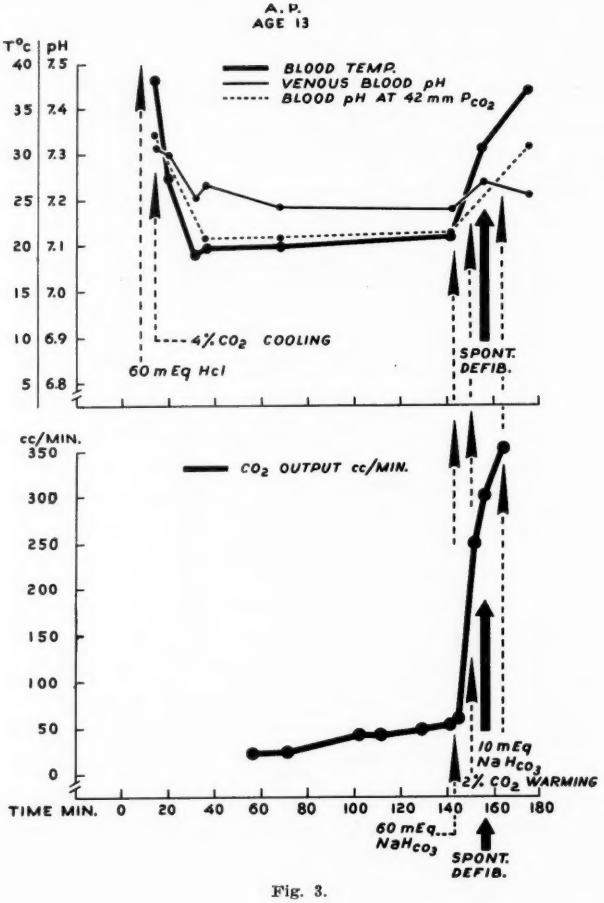

Fig. 3.

in a patient who developed shock during the operation before perfusion with a resulting metabolic acidosis, when perfusion was undertaken and the patient cooled to 22° C., there was a gradual rise in the equilibrated pH, indicating gradual improvement in the patient in spite of the low temperature.

JUSTIFICATION OF ACIDOSIS DURING HYPOTHERMIA

Edmark reached his conclusions regarding the use of induced acidosis largely because of the improved clinical course of his experimental animals.

We explored induced acidosis and came to use it rather routinely also on clinical grounds because, as shown before, the incidence of spontaneous reversion from ventricular fibrillation was higher and, also, because the patients who had been moderately acidotic during cooling "looked better" after rewarming. It is granted,

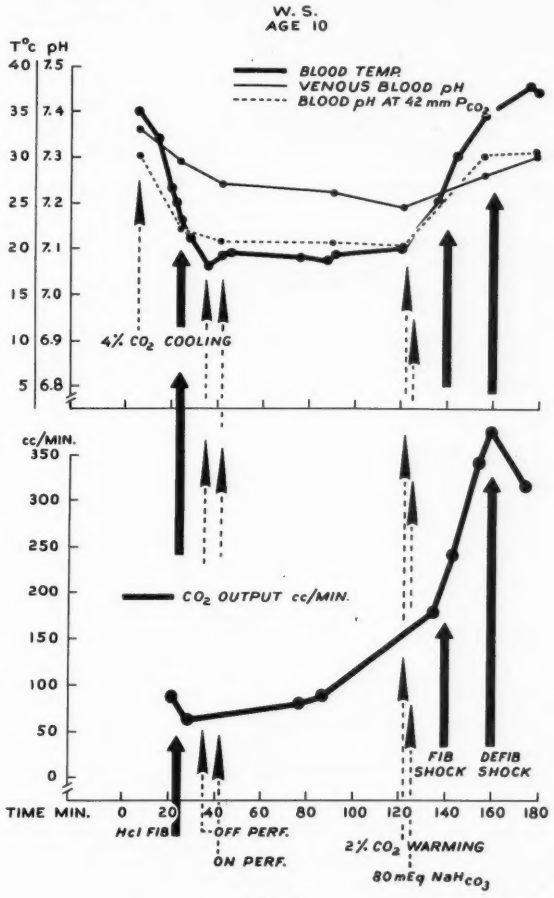

Fig. 4.

however, that clinical observations of this sort are notoriously difficult to control. We will present one possible justification for induction of acidosis during deep hypothermia.

It is standard knowledge that the hemoglobin oxygen dissociation curve shifts to the left on cooling and with alkalosis. The extent of this shift is considerable and, when hypothermia to 16° C. is combined with alkalosis to pH 7.6, the dissociation curve is shifted so far that, at a partial pressure of oxygen of 18 mm. Hg, hemoglobin is still 90 per cent saturated.

It is generally accepted that a tissue pO_2 below 20 mm. Hg represents severe tissue anoxia, yet, at this tension when T = 16° C., pH = 7.6, hemoglobin can unload only 6 to 8 per cent of its combined oxygen. Oxygen transport by hemoglobin is thus severely limited. We are aware that published data suggest that at 16° C. the metabolic rate may be so low that oxygen transport by simple solution in plasma may be adequate.[11] But data for determination of oxygen

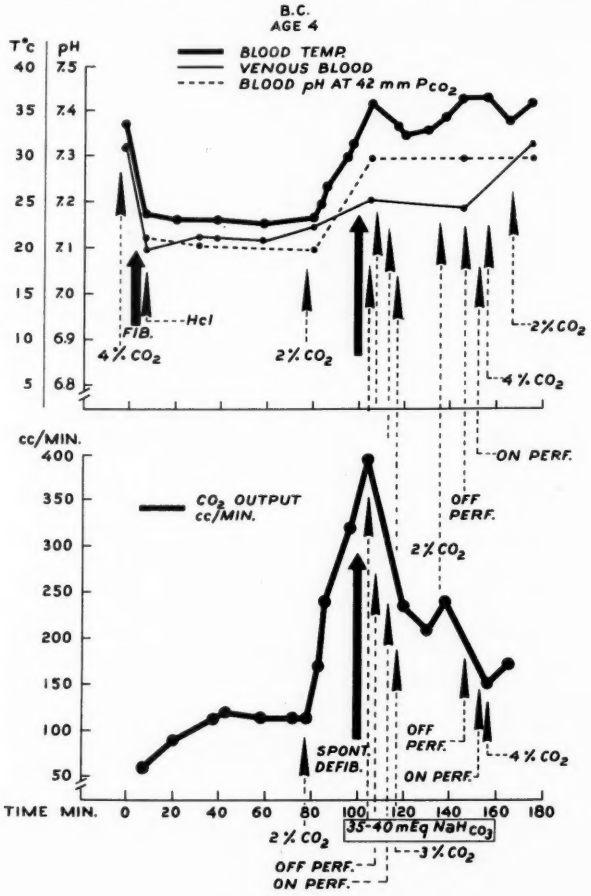

Fig. 5.

uptake during hypothermia in the human being have usually been derived from oxygen uptake or blood arterial and venous oxygen contents. It is, therefore, possible, if blood oxygen transport is reduced, to obtain an artefactually low oxygen uptake, even while severe tissue anoxia is developing and oxygen debt is being built up.

Reptiles show a drop of roughly 50 per cent in metabolism for every 10° C. If this should be true for human beings, at a temperature of 16° C., one would

expect just under one fourth of the normothermic metabolic rate. However, at a pH of 7.6 at 16° C., the transport of O_2 by hemoglobin is reduced to much less than one fourth, if normal tissue pO_2 is maintained. However, if the dissociation curve is "pushed back to the right" by dropping the pH to 7.2, the ratio of oxygen transport to oxygen need is maintained.

These data are illustrated in Fig. 6, which is constructed by extrapolation from accepted data.[12] The vertical line from a pO_2 of 20 mm. Hg (our assumed limit for tissue anoxia) intersects the various curves to demonstrate the percentage of unsaturated hemoglobin available for transport. It is easy to see that at 16° C., pH 7.6 blood will be essentially fully saturated down to tissue pO_2 well below reasonable limits. This may also be demonstrated experimentally. Table I data are presented for a dog cooled to 18° C. at a constant

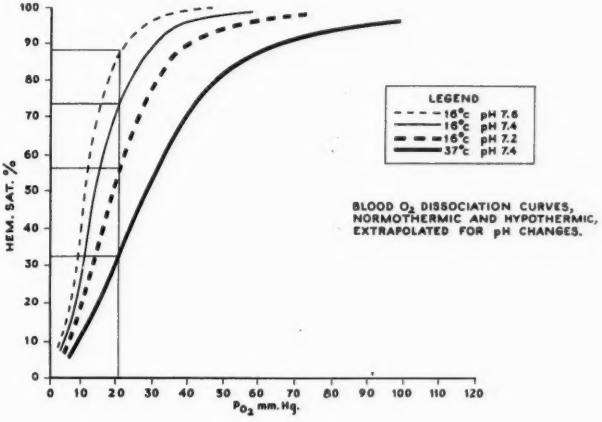

Fig. 6.

flow rate, using a pump-oxygenator. Sample 1 was taken after 30 minutes using a gas mixture of 2.5 per cent CO_2 in the oxygenator before adding any electrolyte. Sample 2 was taken 30 minutes after addition of 30 mEq. HCl, with the oxygenator gas containing 5 per cent CO_2. Sample 3 represents 30 minutes after addition of 30 mEq. $NaHCO_3$, oxygenator gas 2.5 per cent CO_2. Note the increased oxygen uptake on acidification.

TABLE I. DOG WEIGHING 20 KILOGRAMS PERFUSED AT 18° C. (BLOOD FLOW HELD CONSTANT)

	VENOUS pH	ARTERIOVENOUS OXYGEN-DIFFERENCE (VOL. %)
30 min. Oxygenator pCO_2 18 mm.	7.28	0.64
30 min. Oxygenator pCO_2 36 mm. and 30 mEq. HCl added	7.16	2.12
30 min. Oxygenator pCO_2 18 mm. and 30 mEq. $NaHCO_3$ added	7.26	0.33

SPONTANEOUS DEFIBRILLATION IN RELATION TO pH

It is our clinical impression that patients cooled with induced acidosis have less morbidity than those cooled while alkalotic, but, "clinical impression" does not constitute valid evidence. In an attempt to find objective data, we have analyzed our data in regard to the spontaneous conversion of ventricular fibrillation to regular rhythm during rewarming (Table II). There is, of course, no clear evidence that a patient who converts spontaneously is in better condition than a patient who requires vigorous electrical defibrillation. Yet, this is at least an objective measurable phenomenon and it seems likely that a tendency to normal rhythm is a sign of good myocardial health.

TABLE II. INCIDENCE OF SPONTANEOUS DEFIBRILLATION

	NUMBER OF PATIENTS	DEFIBRILLATED SPONTANEOUSLY	PER CENT
Patients cooled with 4% CO_2 in oxygenator	21	3	14
Patients cooled with 6% CO_2 in oxygenator	23	7	30
Patients who received HCl while cooling	13	9	69

Note: Difference between first line and third line is significant at 5 per cent level.

TABLE III. MEANS AND STANDARD DEVIATIONS OF 16 PATIENTS COOLED BELOW 25° C.

	NO. CASES	MEAN LOWEST TEMP. (° C.)	MEAN pH AT COLDEST POINT	MEAN pH AT pCO_2 = 42 MM. WHILE COLD	MEAN pH AT pCO_2 = 42 MM. AT CONVERSION FROM FIBRILLATION
Spontaneous reversion from ventricular fibrillation on rewarming	9	23	7.22 ± .11	7.16 ± .14	7.25 ± .09
Required electric defibrillation on rewarming	7	23	7.30 ± .14	7.22 ± .11	7.34 ± .13

In Table III, 16 cases are summarized. These represent consecutive patients who were cooled to below 25° C., and who had adequate chemical data for study. Nine patients converted spontaneously on rewarming; 7 required electric defibrillation. All these patients, in both groups, were cooled on 4 per cent CO_2, and almost all received at least some HCl during cooling, but, the amount varied rather randomly from patient to patient. It is evident from the table that those patients who converted spontaneously were in general those patients who had the lower blood pH while cool and, also, were those with the lower pH at pCO_2 42 mm. Hg (representing lower serum bicarbonate). However, the difference between the means is not statistically significant, due to the small numbers. However, in Table IV, we have regrouped a larger number of cases in which simple mixed venous pH (while cold) is available. These data are made

up into a fourfold table based on pH above or below 7.3. The difference is significant at the 1 per cent level,[13] with the more acidotic having the highest incidence of spontaneous defibrillation. On a smaller group of patients on whom equilibrated "42 mm. pCO_2" pH determinations were available at the time of conversion from fibrillation during warming (rather than at the coldest point), a similar fourfold table grouping (Table V) gives a difference significant at the 5 per cent level for a relation between low "equilibrated" pH representing essentially low serum bicarbonate and spontaneous defibrillation at the time of defibrillation. These data appear to establish a clear and significant relation between acidosis and conversion from ventricular fibrillation both during the deepest point of cooling and later during rewarming.

TABLE IV. FORTY-SIX PATIENTS COOLED TO UNDER 25° C. DIVIDED BY TYPE OF DEFIBRILLATION AND pH

	NUMBER OF CASES	MIXED VENOUS pH UNDER 7.3 AT COLDEST POINT	PER CENT
Spontaneous reversion from ventricular fibrillation on rewarming	23	16	69.6
Required electric defibrillation on rewarming	23	5	21.7

Note: Difference between groups is statistically significant at the 1 per cent level.

TABLE V. THIRTEEN PATIENTS GROUPED BY EQUILIBRATED pH AT TIME OF CONVERSION FROM VENTRICULAR FIBRILLATION

	pH (AT pCO_2 = 42 MM.)	
	BELOW 7.29 AT CONVERSION	7.29 OR ABOVE AT CONVERSION
Spontaneous reversion from ventricular fibrillation on rewarming	6	1
Required electric defibrillation on rewarming	0	6

Note: Difference between the two groups is statistically significant at the 5 per cent level.

SUMMARY

1. Three hundred and fifty patients have been studied during perfusion-induced hypothermia for cardiac surgery.

2. Carbon dioxide absorption during cooling and its rapid release during rewarming has been demonstrated.

3. In patients cooled under 25° C., an association has been shown between acidosis and spontaneous recovery from ventricular fibrillation on rewarming. Induction of acidosis by the Edmark technique of intravenous infusion of HCl appeared the method of choice.

Acknowledgment is gratefully made of the technical assistance of Mr. Herbert B. Moy and Mr. Eminger Stewart.

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DISCUSSION

DR. HENRY SWAN, II, Denver, Colo.—This certainly is a very interesting and provocative paper if you put it in context with the papers that preceded it, in which the emphasis was upon the postoperative avoidance of any state of acidosis because of its effect upon the circulation. Here is evidence that a rather significant acidosis is of value during the cooling and during the actual operative procedure, and Dr. Gerbode and his group have emphasized the efforts that they take to correct the acidosis as the patient is rewarmed.

I would like to present some data which I believe are strongly confirmatory of the report you have just heard and specifically document the fact that the oxygen dissociation curve can be significantly altered by changing the pCO_2 under conditions of varying temperatures. You will recall the diagram, which was an extrapolation, I believe, that was shown by Dr. Kerth. I would now like to show you a diagram of actual data—measurement of the oxygen dissociation curve as it is influenced by changes in temperature under a constant pCO_2. [Slide] I believe the pCO_2 is 40.

At a constant pCO_2, the oxygen dissociation curve at 37° is here, at 30° here, and at 23° here, and at 15° notice how it has gone to the left and become distorted in the shape of its curve.

[Slide] Let's take the oxygen dissociation curve at 15° and see how it will be affected by change in the pCO_2. Here was the curve that you saw at 40 in the previous slide (20 is essentially normal). If this were occurring in a normal individual it would be over here, but the change that Dr. Gerbode and his team have shown is that if you increase the pCO_2 in this direction—and he mentioned figures up to 75 or 80—you have significantly restored the hemoglobin dissociation curve toward the right and, thus, the ability of the hemoglobin to give up oxygen.

[Slide] These are actual data obtained in the experimental laboratory by Dr. Philip Callaghan, using a tonometer, a rotating disc oxygenator, which proved to be very effective for this purpose. This slide is shown merely to indicate that all of us who use blood perfusion as a cooling mechanism encounter a period of time during that cooling when we may

be subjecting the tissues to significant hypoxia in any given experiment in which the muscle mass is warm, the perfusing blood is cold, and a significant temperature gradient exists.

During this time, when the blood is so very much colder than the tissues that are gradually being cooled because of the inability of the blood to give up oxygen (here you see that at 10° the hemoglobin cannot give up oxygen), it appears likely that you are building up significant acidosis during this period, the acidosis of hypoxia. This may be a good thing if understood in the light of the discussion you have just heard.

[Slide] This final slide shows actual data at given temperatures and at a given pCO_2. Let's take the pCO_2 of 40, which might be reasonable under the conditions of perfusion. Oxygen entering the arterial end of a capillary at roughly 100 mm. Hg, coming out in normal circumstances at 35—normal venous oxygen tension—at temperatures of 37°; under these conditions this blood gave up some 42 per cent of its actual oxygen content. But under similar conditions, let's say at 15°, this hemoglobin can give up only 7 per cent of its oxygen content; if all the tissues were not uniformly that cold, this could result in very significant hypoxia of vital tissues throughout the body.

If the pCO_2 is normal at 20, as Dr. Kerth just mentioned, the hemoglobin simply cannot give up oxygen.

So I think there is no doubt at all, on the basis of this confirmation of the theoretical curves of oxygen dissociation as affected by temperature and pCO_2, that, if we desire adequately to oxygenate tissues at very cold temperatures, we probably must affect either pH or pCO_2 in the direction of acidosis or we will not be able adequately to oxygenate tissues.

The final point is that A-V oxygen differences under these conditions lose their meaning because A-V oxygen differences, which at warm temperatures symbolize whether the tissues are adequately oxygenated, at very cold or very low temperatures may simply indicate that the hemoglobin cannot give up oxygen.

DR. WILLIAM EDMARK, Seattle, Wash.—I am sure that many of you are going to be concerned about the increase in pCO_2 that has previously been reported and there is a certain confusion which exists over the difference between metabolic acidosis and respiratory acidosis. The two are very different. The Henderson-Hasselbalch equation which has been employed for years in calculating the pCO_2 probably does not hold up nor can it be applied in hypothermia, and, in this instance, it becomes necessary to measure the pCO_2 directly, as has been done by Dr. Kerth and his associates.

[Slide] This is a graph of the blood pH versus esophageal temperatures on the first patient in whom we employed 0.3N hydrochloric acid to depress the blood pH during open-heart surgery on Sept. 24, 1959, upon a 50-year-old man with aortic stenosis, who survived and benefited.

In retrospect, it turns out that his curve is rather typical. You will note that during cooling we lowered the blood pH with 0.3N with hydrochloric acid. We then stopped the hydrochloric acid and the pH spontaneously rose. We then depressed it again and, then as we warmed, the pH spontaneously rose.

We find that if we carry on an adequate perfusion, as a rule we do not have to cancel out the hydrochloric acid that we have had to give. Much of this is probably excreted by the kidneys.

[Slide] This is what generally happens during cooling. You will observe that as we cool (and we have plotted here the esophageal temperatures against the arterial blood pH), that if we drop the pH we have less problem with ventricular fibrillation. During warming, if an error has occurred or if metabolic acidosis has accumulated, a shock-like condition will be seen. When this is sensed, at some time sodium bicarbonate can be given to neutralize the metabolic acidosis that has accumulated.

DR. KERTH (Closing).—I would like to thank Dr. Swan for his comments and for the experimental evidence which has supported this theory. Much of our work has been done

on patients, and our approach has been largely a clinical one. We are glad to see that so much work in the experimental laboratory does support it.

There is one thing that I do want to mention; that metabolic acidosis from hypoxia certainly would not be a desirable thing to have happen, even though it might tend to correct itself to some extent by allowing more oxygen to be obtained from hemoglobin. We can very easily neutralize hydrochloric acid with sodium bicarbonate but we can't neutralize the products of metabolic acidosis so easily intravenously.

I would like to thank Dr. Edmark for his comments and, indeed, for his technique.

ALTERATIONS IN BLOOD VOLUME DURING "NORMOVOLEMIC" TOTAL BODY PERFUSION

Robert S. Litwak, M.D. (by invitation), Albert J. Gilson, M.D. (by invitation), Ralph Slonim, M.D. (by invitation), Caspar C. McCune (by invitation), Iris Kiem, M.S., M.P.H. (by invitation), and Howard L. Gadboys, M.D. (by invitation), Miami, Fla.*

ONE of the major factors in the successful conduct of total body perfusion is the maintenance of an adequate blood volume within the patient. It is the purpose of this report to outline the alterations in blood volume seen in 36 patients who underwent open-heart surgery with the use of a pump-oxygenator.

METHODS

Prior to surgery, blood volume was measured by radioiodinated serum albumin (RISA), chromium^{51} labeled red cells, or a combination of both methods. When a single isotope was utilized, the total blood volume plus either the plasma or red cell volumes were measured directly. This was carried out by centrifugation of the blood and direct determination of the activity in the plasma or washed red cell fraction, depending upon the compartment labeled initially.

When a combination of albumin and red cells was used, a single channel system, based on the method of Obrink,[1] was used initially in an attempt to separate the very close photo peaks. This technique was supplanted by individual isotopic measurements, one immediately following the other. The first test sample served as the control for the second isotope.

Conduct of the perfusion was accomplished according to established techniques utilizing gravity flow venous return, a stationary vertical screen oxygenator, roller pumps, and a heat exchanger. Venous pressures were recorded from a catheter inserted in a branch of the cephalic vein. Arterial pressures were measured by means of a catheter passed into the right brachial artery. Continuous observations of these pressures were made before, during, and after cardiopulmonary bypass. During operation, a close record of blood loss and replacement was kept at frequent intervals. The computation of blood loss was based upon: (1) gravimetric determination of blood absorbed on surgical

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*Postdoctoral Research Fellow, National Heart Institute.

sponges, (2) blood drawn for laboratory studies, (3) blood collected in suction bottles, (4) estimation of blood on the surgical drapes, and (5) blood used to fill the tubing of the extracorporeal circuit. An assiduous attempt was made to replace all blood losses quantitatively during the procedure. Following the perfusion, an additional increment of blood (approx. 6 ml. per kilogram) was infused and the subsequent measured blood balance kept positive at that amount in anticipation of unregistered blood loss into the pleural spaces or mediastinum. The patients were weighed on a metabolic scale (accuracy, ± 25 grams) before and after the operation.

Two hours after operation, the blood volume determination was repeated, using the methods outlined above.

TABLE I. DISTRIBUTION OF PATIENTS HAVING BLOOD VOLUME STUDIES

LESION	NO.	DEATHS	PRESUMED MECHANISM OF DEATH
Atrial Septal Defect	7	0	
with anomalous right pulmonary veins	1	0	
with pulmonary stenosis	2	0	
Partial Common A-V Canal	3	1	Marked hypovolemia (Patient 31)
Anomalous Right Pulmonary Venous Drainage With Intact Septa	1	0	
Ventricular Septal Defect	5	2	(1) Severe pulmonary hypertension associated with massive pulmonary insufficiency (congenital absence of pulmonary valve), complete heart block, hypovolemia (Patient 4) (2) Unrecognized subaortic stenosis, hypovolemia (Patient 18)
Tetralogy of Fallot	2	1	Division of anomalous right coronary artery (Patient 6)
Pulmonary Stenosis			
valvular	3	0	
infundibular	1	0	
Mitral Stenosis			
insufficiency	3	0	
Aortic Stenosis			
valvular	7	2	(1) Staphylococcal septicemia (Patient 7) (2) Myocardial infarction (8th postoperative day) (Patient 12)
hypoplastic aortic root	1	1	Inadequate repair, hypovolemia (Patient 38)
	36	7 (19%)	

RESULTS

Pertinent clinical data on the 36 subjects on whom serial blood volume determinations were done are presented in Table I. Seven patients succumbed in the postoperative period. Significant hypovolemia was judged to be the major contributing factor in 4 of these patients.

Table II lists the postoperative deviation from the control blood volume for each patient as established by isotope dilution. The pathologic entities have have been arranged into three groups: (1) left-to-right shunts, (2) right-to-left shunts, and (3) obstructive or regurgitant lesions without shunts. It will be noted that the great majority of patients demonstrated a sizable deficit in the post-perfusion blood volumes. The observed greater blood volume deficit in the group with the left-to-right shunts as compared with the combined right-to-left and non-shunt groups is statistically significant at the 5 per cent level ($P < 0.05$). These data are graphically depicted in Fig. 1. It can be seen that substantial alterations in the plasma and red cell volumes occurred despite the supposedly rigid attempts to maintain "normovolemia."

TABLE II. POSTOPERATIVE BLOOD VOLUME CHANGES

PATIENT NO.	TOTAL BLOOD VOLUME NET CHANGE (ML./KG.)	PLASMA VOLUME NET CHANGE (ML./KG.)	RED CELL VOLUME NET CHANGE (ML./KG.)
	Left-to-Right Shunt		
4	−22.19	− 5.71	−16.48
8	− 8.92	−10.39	+ 1.46
13	−12.93	−13.76	+ 0.82
15	− 5.71	− 6.65	+ 2.94
16	− 7.60	− 5.20	− 1.83
17	−36.10	−21.24	− 6.18
18	−42.38	−11.83	−29.63
19	−20.40	− 8.09	−12.30
22	−28.70	−18.95	− 9.88
24	−21.38	−15.17	− 6.20
26	−17.90	− 9.60	− 8.20
28	−30.40	−22.00	− 8.30
29	−25.70	−12.60	−13.10
31	−66.40	−36.80	−29.60
32	+ 4.10	−10.20	+14.30
33	−48.30	−15.40	−32.80
34	+ 4.90	− 3.50	+ 8.50
	Right-to-Left Shunt		
1	−15.60	− 5.75	−10.70
6	−22.46	+ 2.37	−24.83
23	−12.78	−19.35	+ 6.57
37	+51.20	+29.80	+21.40
	Obstructive or Regurgitant Lesions Without Shunts		
	AORTIC STENOSIS		
3	−27.96	−14.12	−13.84
7	−27.70	−13.99	−13.71
10	− 8.66	− 4.68	− 4.00
12	− 0.77	− 0.58	− 0.18
14	− 1.51	+ 2.65	− 4.16
25	−14.15	− 1.35	−12.80
30	−13.60	− 6.98	− 6.62
38	−19.90	−15.70	− 4.10
	MITRAL STENOSIS-INSUFFICIENCY		
11	− 0.61	+ 0.73	− 1.34
20	−21.36	−10.00	−16.36
36	−13.90	−10.20	− 3.70
	PULMONIC STENOSIS		
2	− 0.96	−13.70	+12.74
21	+ 4.27	+ 3.37	+00.90
27	−20.40	−12.10	− 8.30
35	− 1.60	− 8.90	+14.00

The mean blood volume changes for all patients, regardless of category, are presented in Table III. It is found that after complete volumetric replacement of all calculated blood losses there was a mean net total blood volume loss of 15.40 ml. per kilogram. There was a mean net plasma volume loss of 9.04 ml. per kilogram, and a mean net red cell volume loss of 6.25 ml. per kilogram when compared with preoperative measurements.

TABLE III. MEAN BLOOD VOLUME CHANGES FOR ALL PATIENTS

Total blood volume	−15.40 ml. per Kg.
Plasma volume	− 9.04 ml. per Kg.
Red cell volume	− 6.25 ml. per Kg.

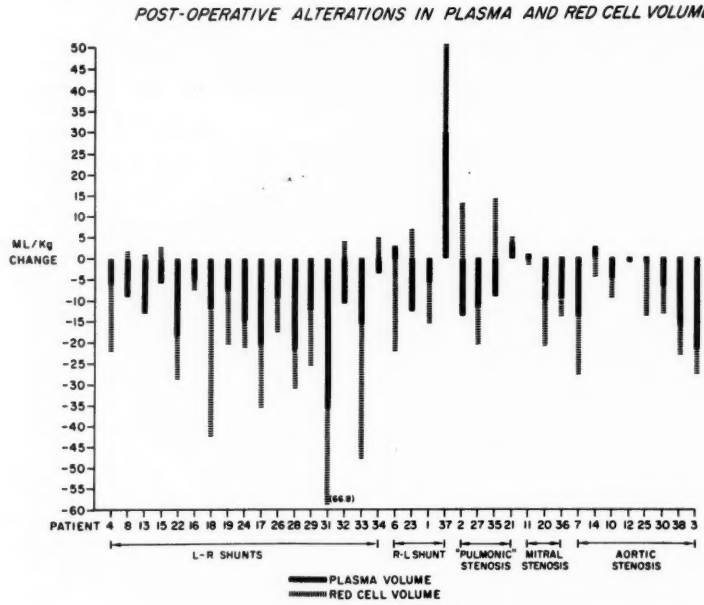


Fig. 1

Comparison of the blood volume changes of the patients who lived and those who died (Patients 4, 6, 7, 12, 18, 31, and 38) reveals a statistically significant greater volume deficit in the latter group ($P < 0.05$). These median deficits were 22.46 ml. and 13.26 ml. per kilogram, respectively.

An attempt was made to evaluate the usefulness of postoperative weight change in maintaining or achieving a "normovolemic" state. Reliable weights were recorded in 29 of the 36 patients. The data were treated by dividing the patients into three groups according to the weight change (post-perfusion weight less than, equal to, or greater than preoperative weight) and plotting the mean blood volume change as the ordinate (Figs. 2, 3, 4). It will be seen that there is no discernible relationship between the postoperative weight change and the

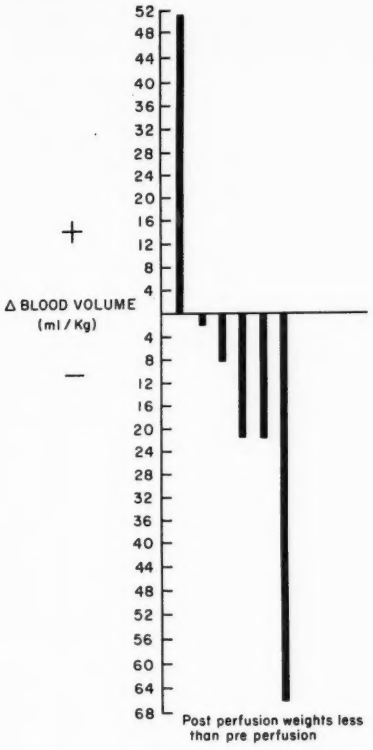
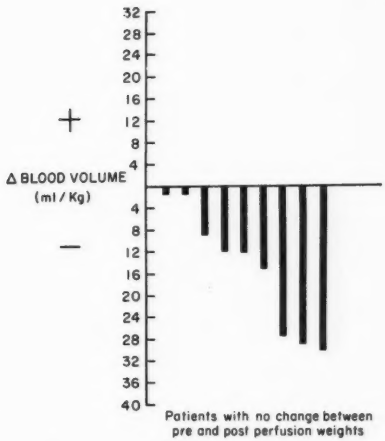


Fig. 2.



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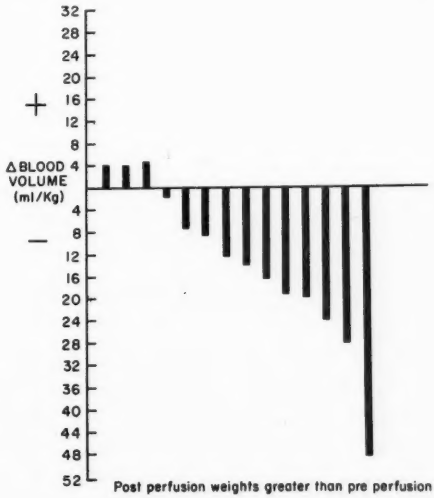

Fig. 4.

Figs. 2, 3, and 4.—Relation of changes in post-perfusion weights to alterations in blood volume.

direction or magnitude of the postoperative blood volume change. In 20 of the 29 patients the weight change was not a reliable guide to the change in blood volume.

Impressed with the significant deviations from the "normovolemic" state that obviously were extant in the postoperative period, we retrospectively examined the venous and arterial pressure data in the hope of finding a predictably direct relationship between one of these variables and blood volume.

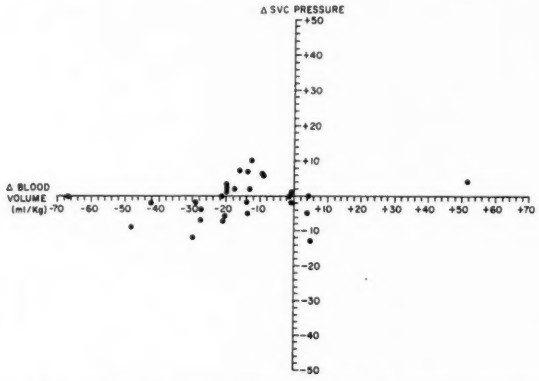

Fig. 5.—Correlation of postoperative blood volume and venous pressure changes early and late during perfusion.

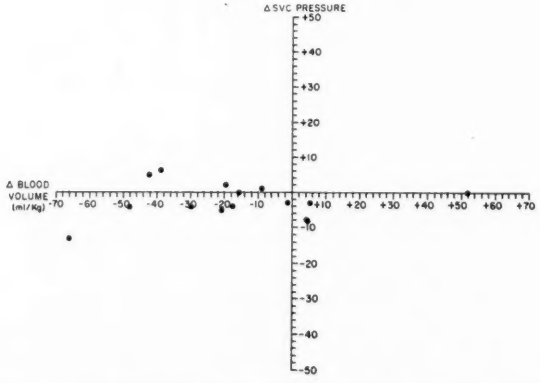

Fig. 6.—Correlation of postoperative blood volume and venous pressure changes before and after bypass.

Pressure data sufficient for statistical analysis were available in 27 of the 36 cases (Table IV). Using the cephalic venous pressure as a measure of superior vena caval pressure, the pressure at the beginning and just prior to termination of total cardiopulmonary bypass was noted and the difference (column A) recorded. A similar venous pressure difference (column B) was measured from changes occurring before the onset and following the termination of bypass.

These data were compared with the blood volume change (Figs. 5, 6). The mean brachial artery pressure changes were treated in an identical fashion (columns C, D) and the data again compared with the postoperative blood volume changes (Figs. 7, 8). Analysis of the correlation between the blood volume change and each of the four variables was done using the Spearman correlation coefficient method. None of the four comparisons was significant, even at the

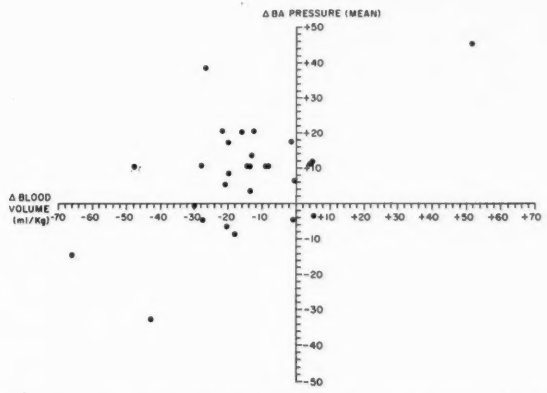

Fig. 7.—Correlation of postoperative blood volume and arterial pressure changes early and late during perfusion.

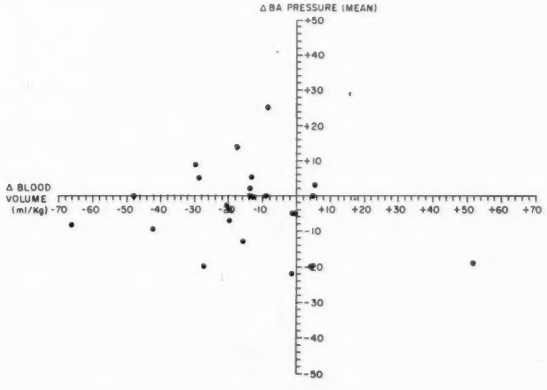

Fig. 8.—Correlation of postoperative blood volume and arterial pressure changes before and after bypass.

10 per cent level ($P > 0.1$). That is, under the conditions of this comparison in which the changes in venous and arterial pressures were considered as single variables, there was no statistically significant correlation with the postoperative blood volume changes.

Attempts were then made to see if analysis of any combination of these variables could provide a predictable guide to the blood volume status. Of the

TABLE IV. CORRELATION OF SYSTEMIC ARTERIAL AND VENOUS PRESSURES AND BLOOD VOLUME CHANGE

PATIENT NO.	BLOOD VOLUME CHANGE (ML./KG.)	SUPERIOR CAVAL PRESSURE CHANGE		MEAN ARTERIAL PRESSURE CHANGE	
		DURING BYPASS (A)	BEFORE AND AFTER BYPASS (B)	DURING BYPASS (C)	BEFORE AND AFTER BYPASS (D)
1	−15.60	+ 7	0	+20	−13
2	− 0.96	− 2	− 3	+ 6	− 5
3	−27.96	− 7	*	+35	*
7	−27.70	− 3	*	− 5	−20
8	− 8.92	+ 6	+ 1	+10	0
10	− 8.66	+ 6	*	+10	+25
12	− 0.77	+ 1	*	− 5	− 5
13	−12.93	+ 2	*	+13	0
18	−42.30	− 2	+ 5	−33	− 9
19	−20.40	− 6	*	− 7	*
21	+ 4.27	0	− 8	+10	0
22	−28.70	− 1	+ 6	+10	+ 5
23	−12.78	+10	*	+20	*
24	−21.38	− 7	− 5	+ 5	− 3
25	−14.15	− 2	*	+10	+ 2
26	−17.90	+ 2	− 4	− 9	+14
27	−20.40	+ 2	+ 2	+ 8	− 7
28	−30.40	−12	− 3.5	− 1	+ 9
30	−13.60	+ 7	*	+10	0
31	−66.40	0	−13	−15	− 8
32	+ 4.10	− 5	− 8	+10	−20
33	−48.30	− 9	− 4	+10	0
34	+ 4.90	−13	− 3	− 4	+ 3
35	− 1.60	0	− 3	+17	−22
36	−13.90	− 5	*	+ 3	+ 5
37	+51.20	+ 4	0	+45	−19
38	−19.90	+ 3	*	+17	− 4

*No data.

combinations studied,* one subgroup (No. 7) proved to be of borderline statistical significance, and the others were statistically insignificant. When the changes of venous and arterial pressure from the early to late periods during perfusion occurred in the same direction there was a correlation at the 5 per cent level between the mean change in the pressures and the change in blood volume ($P = 0.05$). However, this was a highly selected group comprising only 14 of the 27 patients (52 per cent). Moreover, even in this group from which virtually half the patients were excluded, a statistical correlation was just barely discernible. If one further subdivides this group and considers only those patients whose venous and arterial pressures *both rose* from early to late periods during perfusion (9 cases), 8 of these still had significant postoperative blood volume deficits averaging −14.09 ml. per kilogram. When the analysis was not limited to cases in which the venous and arterial pressures changed in the same direction during perfusion there was no longer any statistically significant correlation ($0.1 > P > 0.05$).

*The data were analyzed statistically in the following combinations (see Table IV):
1. Venous pressure change during bypass (A) vs blood volume change (BVC) (all patients).
2. Venous pressure change before and after bypass (2) vs BVC (all patients).
3. Arterial pressure change during bypass (C) vs BVC (all patients).
4. Arterial pressure change before and after bypass (D) vs BVC (all patients).
5. Mean of A + C (all patients) vs BVC.
6. Mean of B + D (all patients) vs BVC.
7. Mean of A + C (limited to cases in which A and C varied in same direction) vs BVC.
8. Mean of B + D (limited to cases in which B and D varied in same direction) vs BVC.
9. Mean of A + B+C+D (all patients) vs BVC.
10. Mean of any three of A,B,C,D where variation in same direction vs BVC.

DISCUSSION

The radioisotopic methods for the determination of blood volume in our hands have shown a reproducibility of ± 4 per cent. Because of this degree of accuracy we have utilized this method to assess the adequacy of blood volume replacement in open heart operations. This approach has also been utilized by others, including Kaplan,[2] Carr,[3] and Ausman[4] and their associates.

Despite assiduous attempts to maintain a constant blood volume in the patients, this was not accomplished in the majority of the cases. This is exemplified by the finding that 23 of the 36 patients (64 per cent) had significant postoperative hypovolemia with a deficit consisting of more than 10 ml. per kilogram. It is of interest that there was a significantly greater blood volume deficit in those patients having left-to-right shunts when compared with those with right-to-left shunts and no shunts.

The lack of relationship of post-perfusion weight changes to blood volume alterations has been repeatedly observed. It is noteworthy that in 20 of 23 patients there was a loss of blood volume with either a gain or no change in weight. This suggests that there may be sequestration of blood in vascular areas not reached by the isotopes postoperatively or that fluid is being transferred into the extravascular space during the perfusion. The latter hypothesis is consistent with the observation of Sturtz and co-workers[5] that serum water concentration decreases steadily during perfusion. In any event, it can be seen that the postoperative body weight does not adequately reflect the postoperative blood volume status of the patient.

Hypovolemia was believed to be of major significance in the death of 4 patients in the postoperative period. With the exception of one patient who died from a myocardial infarction 8 days after open aortic valvuloplasty employing anoxic arrest, in all of the fatalities there were blood volume deficits of 19.9 ml. per kilogram or more. The greater blood volume deficits in this group, when compared with the blood volume alterations in those patients who survived, were statistically significant, but it did not necessarily follow that all patients with losses exceeding this amount died. It is probable that the magnitude of the procedure and the adequacy of the repair were also important in the outcome.

Many approaches have been utilized in attempting to achieve normovolemic perfusion. Probably the most widely used methods involve restoration of adequate arterial pressure, venous pressure, or a combination of the two at the completion of the perfusion. The data contained herein indicate that no single one of these variables is a reliable criterion. Moreover, even when an attempt is made to utilize two or more of these phenomena in all patients the estimation of blood volume changes is still highly unreliable. Only when there were changes in arterial and venous pressures in the same direction and when these changes occurred during the actual perfusion was there a relationship between pressure changes and blood volume change. However, even in this highly selected group comprising only half of the series, there was but borderline statistical significance ($P = 0.05$). It is noteworthy that, even when this highly selected group

was further subdivided and only those patients were considered whose venous and arterial pressures *both rose* from early to late periods during perfusion, 89 per cent of these (8 of 9 patients) still had substantial blood volume deficits averaging –14.09 ml. per kilogram.

Another attractive approach to the maintenance of normovolemia has been the use of a constant arterial flow rate at a preselected level allowing the patient to control (automatically) his own blood volume.[6, 7] Our experience with this method is insufficient to permit any conclusions. Possible pitfalls are illustrated by the sequence of events in a patient undergoing surgical repair of mitral insufficiency (Fig. 9). A predicted flow rate of 2.4 L./M.²/min. was rapidly

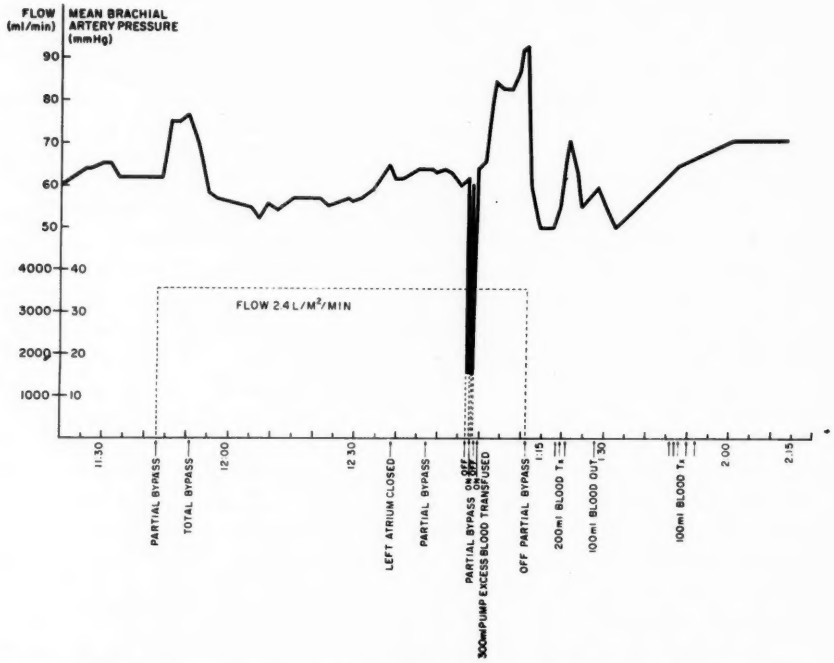

Fig. 9.—Brachial artery mean pressure *(solid line)* and arterial flow *(broken line)* in clinical case employing preselected fixed flow and automatic control of blood volume (see text).

attained and kept constant throughout the entire perfusion. The mean arterial pressure remained at a satisfactory level throughout. Despite this, the patient did not pick up her computed blood losses from the extracorporeal circuit. In fact she returned an additional 300 ml. of blood to the reservoir. On discontinuing perfusion, there was a precipitous arterial pressure fall to 15 mm. Hg. Bypass was quickly re-established at the predicted flow rate with restoration of the previous arterial pressure. This sequence was repeated with identical results. After infusion of 300 ml. of blood it was possible to discontinue bypass at a mean brachial arterial pressure approximately 10 mm. Hg below the preperfusion level. In the ensuing 30 minutes an additional 1,000 ml. of blood was

infused to replace computed blood loss. Despite this infusion, the postoperative blood volume determination in this patient still revealed a total deficit of 594 ml. (12.4 ml. per kilogram).

It is perhaps regrettable that this report provides more questions than answers. There is general agreement that it is desirable to maintain a normovolemic state during and after perfusion although this concept has not been entirely documented. It may be that in circumstances in which a large central volume has been reduced by an effective surgical procedure the ideal postoperative "normovolemic" state may be materially less.

There is no question that measurement of venous and arterial pressures during perfusion provides essential information regarding the general clinical status of the patient but it is clear that major blood volume discrepancies may exist without comparable alterations in those pressures. It is equally clear that inadequacy of myocardial function due to any cause in the postoperative period can lead to changes in venous and arterial pressures unrelated to changes in blood volume, further compromising the use of these variables in assessing adequacy of blood replacement at that time.

It is emphasized that this report is not intended to deprecate the immense value of systemic pressure managements at all times in the successful recovery of the patient after open heart surgery but it is essential to realize that these measurements may be perfectly normal in the postoperative period (or indeed even be elevated) in the face of substantial blood deficits. It is clear from the data presented that significant deficits in themselves need not always be lethal but in patients who have had major cardiac insults the superimposition of serious hypovolemia probably makes the difference between survival and death. Until a predictable means of maintaining normovolemia is developed, hypovolemia will continue to present a threat to the life of the patient undergoing cardiopulmonary bypass.

SUMMARY

1. Pre- and postoperative blood volume determinations were performed on 36 patients undergoing open heart operations with extracorporeal circulation.

2. There was an average postoperative blood volume deficit of 15.40 ml. per kilogram. The plasma and red cell deficits were 9.04 ml. and 6.25 ml. per kilogram, respectively. This was so despite careful attempts to replace all blood loss.

3. Hypovolemia appeared to be a significant factor in the death of 4 of 7 patients. The median blood volume deficit in the 7 patients who died was 22.46 ml. per kilogram, whereas the median value for the survivors was 13.26 ml. per kilogram. The difference is statistically significant ($P < 0.05$).

4. There was no discernible correlation between postoperative weight changes and blood volume alterations.

5. Changes in venous pressures, arterial pressures, or a combination of the two bore no statistically significant relationship to postoperative blood volume

changes with one exception. Only when arterial and venous pressures deviated in the same direction *during* perfusion was there correlation of borderline statistical significance ($P = 0.05$).

6. This report is not intended to deprecate the use of venous and arterial pressure measurements during and after perfusion since these provide essential information regarding the clinical status of the patient.

7. A substantial blood volume deficit need not necessarily be lethal but, in a patient whose heart has been seriously traumatized, hypovolemia probably makes the difference between survival and death.

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(For Discussion, see page 494)

A STUDY OF THE CAUSES OF 60 DEATHS FOLLOWING TOTAL CARDIOPULMONARY BYPASS

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*Jean P. Despres, M.D., F.R.C.S. (C), ** (by invitation), and*
*Riccardo Benvenuto, M.D.*** (by invitation), Edmonton, Alberta*

THIS study was undertaken to obtain an over-all view of the major factors which cause death following total cardiopulmonary bypass for the repair of congenital and acquired diseases of the heart.

Sixty deaths occurred in 250 patients subjected to extracorporeal circulation at the University of Alberta Hospital, Edmonton, Canada. This study covers the period of 4½ years from September, 1956, to March, 1961.

Seventy-five of the 250 patients studied underwent total cardiopulmonary bypass by means of a bubble oxygenator and Sigmamotor pumps as developed by Lillehei and DeWall at the University of Minnesota (Fig. 1).

One hundred and seventy-five patients were subjected to open-heart surgery using a rotating disc oxygenator (Pemco) and De Bakey roller-type pumps, as described by Kay and Cross (Cleveland) and modified by Gross (Boston). Of these 175 patients, 116 had congenital defects. Nineteen of these patients died, resulting in a mortality rate of 16.3 per cent. Fifty-nine patients suffered from acquired heart disease and 18 of these patients failed to survive, providing a mortality rate of 30.5 per cent.

A review of the 60 patients who failed to survive operation was undertaken and an attempt was made to determine one major cause of death for each patient. Other factors played prominent roles in many patients but, after careful assessment, the classification as shown in Fig. 2 was created.

DIAGNOSTIC FACTORS

In this subdivision, 11 of 60 deaths were classified. Those patients considered to represent poor selection by cardiologic assessment were grouped with 6 patients who at operation presented uncorrectible lesions.

From the Department of Surgery, University of Alberta Hospital, Edmonton, Alberta, Canada.

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A. *Selection—5 patients:* These patients included one with mitral stenosis —regurgitation, severe preoperative liver failure; one with patent ductus (1-month-old moribund infant); and 3 with Grade IV cardiac disease with giant hearts and "stiff lungs."

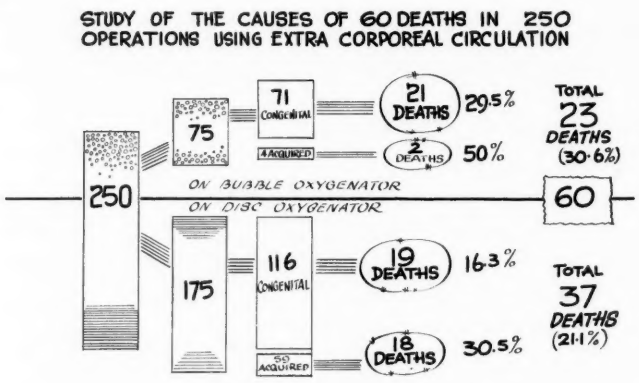

Fig. 1.

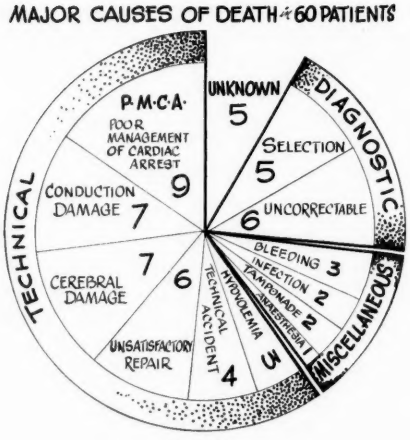

Fig. 2.

B. *Uncorrectible—6 patients:* There was one patient each with (1) common ventricle with corrected transposition, (2) tricuspid and right ventricular atresia, (3) tricuspid stenosis and regurgitation, (4) Cor triloculare, (5) Tetralogy of Fallot—diminutive left ventricle, and (6) destroyed mitral valve—no prosthesis available then.

SURGICAL DAMAGE TO THE CONDUCTING MECHANISM

Seven patients died directly as a result of damage to the conducting mechanism. These patients are listed in Table I.

TABLE I

NO.	DATE	DURATION OF BYPASS (MIN.)	TIME OF DEATH	LESION	AGE (YEARS)
1	1957	64	2 da.	2 ventricular septal defects, atrial septal defect, pulmonary hypertension	12
2	1958	70	1 da.	Tetralogy of Fallot	4
3	1959	82	3 da.	Ventricular septal defect; corrected transposition	26
4	1959	125	O. R.	Tetralogy of Fallot	2
5	1960	139	8 da.	Tetralogy of Fallot	46
6	1960	200	O. R.	Repeat ventricular septal defect	2½
7	1960	113	O. R.	Ventricular septal defect	2

TECHNICAL ACCIDENTS

In four instances in the 250 patients subjected to extracorporeal circulation, a technical accident was directly the cause of death (Table II).

TABLE II. TECHNICAL ACCIDENTS

AGE (YEARS)	YEAR	DEATH	LESION	TYPE OF ACCIDENT
1	1958	O. R.	Total anomalous venous return	External iliac cannula pulled out
28	1959	O. R.	Aortic insufficiency, mitral insufficiency	Aortic tear
16	1959	48 hr.	Tetralogy of Fallot	Femoral cannula pulled out
53	1960	O. R.	Plastic aortic valve replacement	L. A. vent pulled out with tear

HYPOVOLEMIA

The problem of hypovolemia following bypass resulted in death in three instances in the 250 patients studied and contributed to 3 of the 60 deaths. Two of these occurred in 1956 and one in 1957. There have been no cases in recent years in which this factor could be listed.

POOR MANAGEMENT OF ELECTIVE CARDIAC ARREST (TABLE III)

In 9 patients of the 60 deaths studied, poor management of elective cardiac arrest was identified as the major cause of death. In 7 of these patients, elective cardiac arrest was induced by using acetylcholine (10 mg. per kilogram of body weight) which was injected into the root of the aorta. The aorta and pulmonary artery were cross-clamped together and no vent was used. This is mentioned in order to be strongly condemned in light of our more recent knowledge.

In 2 patients, elective cardiac arrest of excessive length was identified as the major cause of death.

TABLE III. POOR MANAGEMENT OF ELECTIVE CARDIAC ARREST

AGE	DATE	LENGTH OF BYPASS (MIN.)	DEATH	LESION	OTHER FACTORS
Acetylcholine Arrest—7 Patients—No Vent					
5 yr.	1956	39	10 hr.	Ventricular septal defect + pulmonary hypertension	Pulmonary vascular changes
6 yr.	1957	22	30 hr.	Ventricular septal defect + atrial septal defect	Partial breakdown of repair
13 yr.	1957	47	3 da.	Ventricular septal defect + mitral stenosis + pulmonary hypertension	Pulmonary vascular changes
4 yr.	1957	71	3 da.	Tetralogy	Superior vena cava pressure high during bypass
9 yr.	1958	115	O. R.	Aortic insufficiency, ventricular septal defect; trauma	Poor repair
11 mo.	1958	24	10 hr.	Ventricular septal defect	Too young
6 mo.	1958	35	12 hr.	Ventricular septal defect	Too young
Anoxic Arrest—2 Patients—No Vent					
14 yr.	1958	121	O. R.	Mitral insufficiency + aortic insufficiency	Large heart Fair repair
43 yr.	1959	85	27 hr.	Mitral insufficiency + aortic insufficiency	Large heart Fair repair

CEREBRAL DAMAGE (TABLE IV)

Severe cerebral damage was the cause of death in 7 of the 60 patients who died. Air embolus was the cause in 4 of these. Calcium embolus proved to be the cause in 2 patients. In one patient with tetralogy of Fallot, although the defect was repaired satisfactorily, the child never regained consciousness. The electroencephalogram became flat as soon as bypass commenced. Microbubbles due to the bubble oxygenator were suspected as the cause.

TABLE IV. CEREBRAL DAMAGE (7 PATIENTS)

NO.	AGE	DATE	DEATH	LESION	FACTOR
1	18 mo.	1957	4 hr.	Tetralogy of Fallot	Microbubbles
2	13 mo.	1958	O. R.	Tetralogy of Fallot	Air, via right atrial catheter
3	18 yr.	1958	10 da.	Mitral insufficiency	Air
4	49 yr.	1959	4 da.	Mitral insufficiency	Calcium
5	50 yr.	1959	1 da.	Coarctation + Cdle. aortic stenosis	Calcium
6	53 yr.	1959	3 da.	Mitral insufficiency, mitral stenosis	Air
7	53 yr.	1960	O. R.	Mitral insufficiency, mitral stenosis	Air

MISCELLANEOUS CAUSES

Eight of the 60 deaths studied were grouped as miscellaneous. Of the 3 cases in which bleeding was believed to be the major cause of death, one was massive oozing from multiple adhesions in lung, one from a cut end of a coronary artery, recognized too late, and the other from a tear in the medial side of the right atrium due to the pulling through of a cross-plicating stitch in the tricuspid annulus.

Two patients died directly as a result of infection.

Two patients died from tamponade which was delayed 4 days and 10 days, respectively, and went unrecognized until necropsy.

In one instance, in 250 patients anesthetized for open-heart surgery, cardiac arrest on intubation resulted in death of the patient.

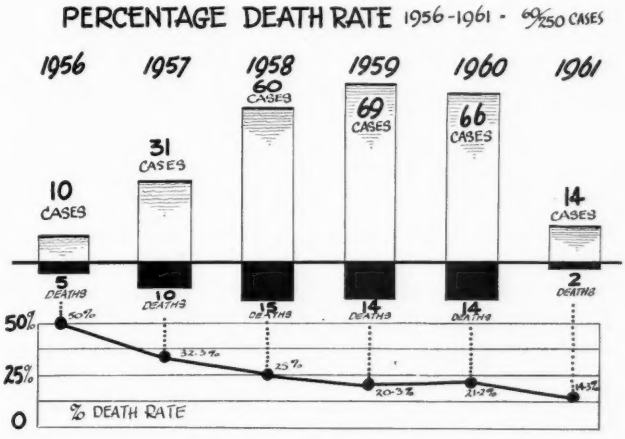

Fig. 3.

UNKNOWN CAUSES

In 5 of the 60 deaths studied, a final decision as to cause of death could not be reached. In each case the repair was satisfactory (Table V).

TABLE V. UNKNOWN CAUSES OF DEATH—5 PATIENTS

1. Congenital mitral stenosis, age 7 yr.; excellent repair; excellent drop in LA pressures. Death fourteenth postop. day. Suspect unrecognized failure.

2. Ventricular septal defect and pulmonary hypertension, age 2 yr.; good repair; good run; no elective arrest. Sudden death 13 hr. postop. Suspect left ventricular failure.

3. Tetralogy of Fallot, age 6 yr.; excellent repair; never able to maintain blood pressure. Died 8 hr. Suspect minute fibrin emboli.

4. Mitral insufficiency, age 24 yr.; excellent repair; no elective arrest. Died at home in sleep 24 days postop. Suspect necrosis of papillary muscle.

5. Mitral insufficiency, age 35 yr.; satisfactory repair; no elective arrest. Restlessness, sudden left ventricular failure 30 hr. postop.

DISCUSSION

The classification of the major cause of death for each of the 60 patients in this series proved to be just as difficult as it was thought to be prior to the study.

It was noted that extracorporeal circulation itself did not contribute as much to mortality, even in the earlier cases, as had been expected. It appeared that surgical causes including failure to correct the lesion adequately, as well as poor management of elective cardiac arrest, was most often the major factor.

Year by year there was a gratifying fall in total mortality, as shown in Fig. 3. Better selection of patients does not appear to play as prominent a role as improved surgical management.

Leaflet aortic valve replacements have saved at least 5 patients who otherwise would undoubtedly have contributed to an increase in mortality in this series.

It is projected that an additional decrease in the mortality will occur as total mitral valve replacements become available.

In this series, within the last 18 months, management of elective cardiac arrest using local myocardial hypothermia with proper left ventricular venting has played a great role in the improvement of survival rate, contributed to better anatomic repair, and decreased the incidence of air embolization.

In retrospect, a re-analysis of the 60 patients who failed to survive, with a view to an estimation of what would have happened using our present knowledge, would drop the mortality to 27 deaths in 250 patients. This figure of 10 per cent mortality is close to the 14 per cent mortality in our recent series.

SUMMARY

An analysis has been made of the major causes of 60 deaths resulting from the use of extracorporeal circulation in 250 patients for the correction of congenital and acquired defects of the heart.

DISCUSSION

(PAPERS BY LITWAK [PAGE 477] AND CALLAGHAN [PAGE 489] AND THEIR ASSOCIATES)

DR. JAMES B. LITTLEFIELD, Charlottesville, Va.—I wish to discuss Dr. Callaghan's presentation and emphasize the need for adequate left-heart decompression during cardiopulmonary bypass. Effective drainage of the left side of the heart is particularly important in patients with a high collateral pulmonary blood flow and acquired aortic and mitral valvular disease.

[Slide] Here we see the acute pulmonary hypertension (above 60 mm. Hg) which occurs experimentally after occluding both the pulmonary artery and aorta during cardiopulmonary bypass, in the presence of a high bronchial artery flow. Gross pulmonary edema and hemorrhage are evident after 10 minutes of sustained pulmonary hypertension; these changes are probably irreversible.

[Slide] This photomicrograph of the lung shows extensive peribronchial, perivascular, and alveolar hemorrhage. These changes result from sustained pulmonary hypertension during complete pump dependency when left-heart decompression is either inadequate or absent.

[Slide] This slide demonstrates, in the dog, how rapidly pulmonary hypertension (above 30 mm. Hg) may develop, after complete pump dependency, if cardiopulmonary bypass is discontinued before adequate recovery of the left ventricle, or after a short period of cardiac arrhythmia.

Prolonged periods of partial pump dependency, with decompression of both the right and left sides of the heart, may be mandatory at the completion of an open-heart procedure. This decompression is particularly important in the patient with severe myocardial disease after an open-heart procedure on the aortic valve.

DR. ARTHUR M. VINEBERG, Montreal, Quebec.—Our own experience with total pulmonary bypass has been largely confined to adults with valvular acquired lesions. Of 26 patients undergoing operation for acquired valvular lesions, with or without associated valvular disease, there were 7 deaths. In the group there were 2 cases of mitral insufficiency and significant aortic insufficiency, in one of which there was a completely destroyed mural leaflet which required prosthetic correction.

Of 7 patients with mitral insufficiency and stenosis there were two deaths; one patient had no aortic leaflet and the other had a heart dilated in every chamber.

There were 8 cases of complicated mitral stenosis; 6 of these patients had had from one to three previous operations. Two of these patients died and in both cases the mitral leaflet function after commissurotomy was extremely poor due to calcifically contracted and partially destroyed valves. One patient with calcific mitral stenosis, aortic stenosis, and insufficiency had an excellent correction of both lesions. He was 58 years of age and died in the recovery room in the early hours of the morning from a sudden ventricular fibrillation.

From our total experience, it would seem that once the patient is placed on extracorporeal circulation, it is extremely important that adequate mitral valve function be obtained and that any coexisting lesion of the mitral valve be likewise corrected if the patient is to survive. Evaluation of myocardial reserve is difficult.

DR. HOWARD A. FRANK, Boston, Mass.—Dr. Litwak's very clear presentation shows that there is no way of knowing the blood volume change during cardiopulmonary bypass except by measuring it, and, therefore, it is fortunate that there is now available a convenient and nearly automatic, accurate apparatus that will tell us the blood volume in 15 minutes, as often as necessary, in the operating room, recovery room, and at the bedside. This apparatus was developed by a group of engineers and surgeons, led by Dr. John Williams of our Department.

I will not take time now to describe the apparatus; a paper on it by Dr. Williams and Dr. Fine has recently been published in the *New England Journal of Medicine*, 264: 842, 1961. I will say only that we have found the apparatus useful and reliable in the daily work of our surgical service.

DR. LAURENCE RIVKIN, San Francisco, Calif.—I would like to comment briefly on the treatment of patients who died after cardiac operations. As Dr. Callaghan has demonstrated, many of the deaths were related to functional and metabolic changes which were potentially of a reversible type.

Some months ago we instituted a study of external cardiac compression, as described by Dr. Kouwenhoven. Our laboratory experience confirmed the efficacy of the technique.

To minimize the chest wall trauma, we have utilized a slower rate of compression than originally advocated. [Slide] As you can see here, the cardiac output during external compression of the heart in the dog was maintained at about 50 per cent, whether we did the

cardiac compression at the rate of 60 per minute or 30 per minute. There were significantly fewer broken ribs and it is much easier on the operator utilizing the slower rate. Incidentally, after defibrillation of the dogs, their cardiac output ran about 42 per cent of the basal rate.

We have been educating our house staff and nursing staff in the technique of total cardiac compression and we prepared this poster for their education. This is a sort of do-it-yourself poster which we are distributing to our local friends, so that our nurses will know how to save our patients.

Our results have been gratifying. We have had 2 adult patients resuscitated by our nurses in the recovery room. Both had open-heart operations for acquired disease, and cardiac standstill was verified by observing asystole on a monitoring oscilloscope. Both patients have survived.

In addition, we had 10 other surviving patients after closed chest cardiac resuscitation, with or without defibrillation, which occurred outside the operating room.

HOMOTRANSPLANTATION OF THE AORTIC VALVE

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Denton A. Cooley, M.D., and Michael E. De Bakey, M.D.,
Houston, Texas

CARDIAC valve homotransplantation came as a logical evolvement of the successful use of vessel homografts. Cusp homografts have been used in both the tricuspid and the aortic valves. From such studies have come conflicting reports.[26, 36, 39] Many attempts to homotransplant the entire aortic valve have met with failure due to hemorrhage[6, 20] or to degeneration of the cusps over a period of time.[6, 7, 20, 25] However, in only one of these studies was a need for the valve created, and here the aortic insufficiency produced was only temporary in the majority of the animals.[25] Such an experiment cannot be considered conclusive.[24]

Hemorrhage from aortic valve homografts can be prevented by various technical maneuvers.[25] Murray has shown experimentally that aortic valve homografts will continue to function in the presence of permanent aortic insufficiency,[34] and has utilized such valves successfully in several human patients.[32, 33, 34] As yet no one has attempted to confirm these findings.

The fate of valve homografts is not clear. In such a valve are many inherent advantages. Although vessel grafts of various synthetic materials are now being used with increasing frequency in arterial reconstruction, no *entirely satisfactory synthetic* valve is available. In an effort to clarify the usefulness of aortic valve homografts in a hemodynamic environment which requires the presence of a valve, the following study was undertaken.

METHOD

Mongrel donor dogs, similar in weight to recipient animals, were sacrificed, and the hearts removed under sterile conditions. The aortic valve was excised in such a manner as to include 1.0 cm. of ascending aorta and a small amount of proximal myocardium. A 1.0 to 1.5 cm. segment from the ascending aorta was meticulously sutured as a cuff to the myocardial side of the valve with simple, running 5-0 arterial silk. The coronary orifices were oversewn with 5-0 arterial silk. The valve was then refrigerated from 2 to 48 hours in an antibiotic containing electrolyte solution similar to that described by Gross.[18]

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Mongrel recipient dogs, varying in weight from 11.3 to 29.5 kilograms, were anesthetized with Nembutal sodium, 30 mg. per kilogram. Intermittent positive pressure oxygen was administered through an endotracheal tube. In the lateral position the chest was entered through the fourth left intercostal space, utilizing aseptic technique. A 4 to 5 cm. segment of the proximal descending thoracic aorta was freed, ligating one or two pairs of intercostal arteries. The aorta was occluded proximally and distally with arterial clamps, and a segment of the same length as that of the valve to be inserted was excised. A previously prepared aortic valve homograft was then sutured in place using simple, running 5-0 arterial silk (Fig. 1). Neither hypothermia[37] nor pump bypass[31] was used, as the period of aortic occlusion was only 20 to 25 minutes and no difficulty was noted from aortic occlusion of this duration. After the valve was in place, clamps were slowly released, and stored blood was given as indicated. For a brief period there was often some bleeding from the myocardial suture line, but this readily stopped if the clamps were released slowly. Only one operative death could be attributed to hemorrhage, and this was the first animal in which the procedure was carried out.

Fig. 1.—Aortic valve homograft sutured into descending thoracic aorta.

After allowing sufficient time for the animals to stabilize from this procedure, generally 10 to 15 minutes, aortic insufficiency was created by a technique previously reported.[11] The left subclavian artery was divided 2 to 3 cm. from the aortic arch, and the distal cut end ligated. Under control of a tourniquet, a bent crochet hook was introduced into the aortic arch through the proximal cut end of the subclavian artery. This was passed into the sinus of the posterior cusp of the animal's own aortic valve, guided by a finger along the outer posterior wall of the intrapericardial aorta. The hook was punched through the cusp, and the cusp grasped and avulsed. The hook was removed, and the subclavian artery ligated.

The chest was closed, drainage catheters were removed, and the animals returned to their cages. Penicillin and streptomycin were given for 5 days. At intervals of 1, 3, 6, 9, and 12 months after operation, arterial pressure tracings were taken simultaneously proximal (right brachial artery) and distal (femoral artery) to the homograft valves, utilizing Statham strain gauge manometers and an Electronics for Medicine recorder. At the time of sacrifice, the animals' own aortic valve was examined for the presence of insufficiency. The homograft valves were tested for competence to water pressure, the leaflets examined, and slides made for microscopic study.

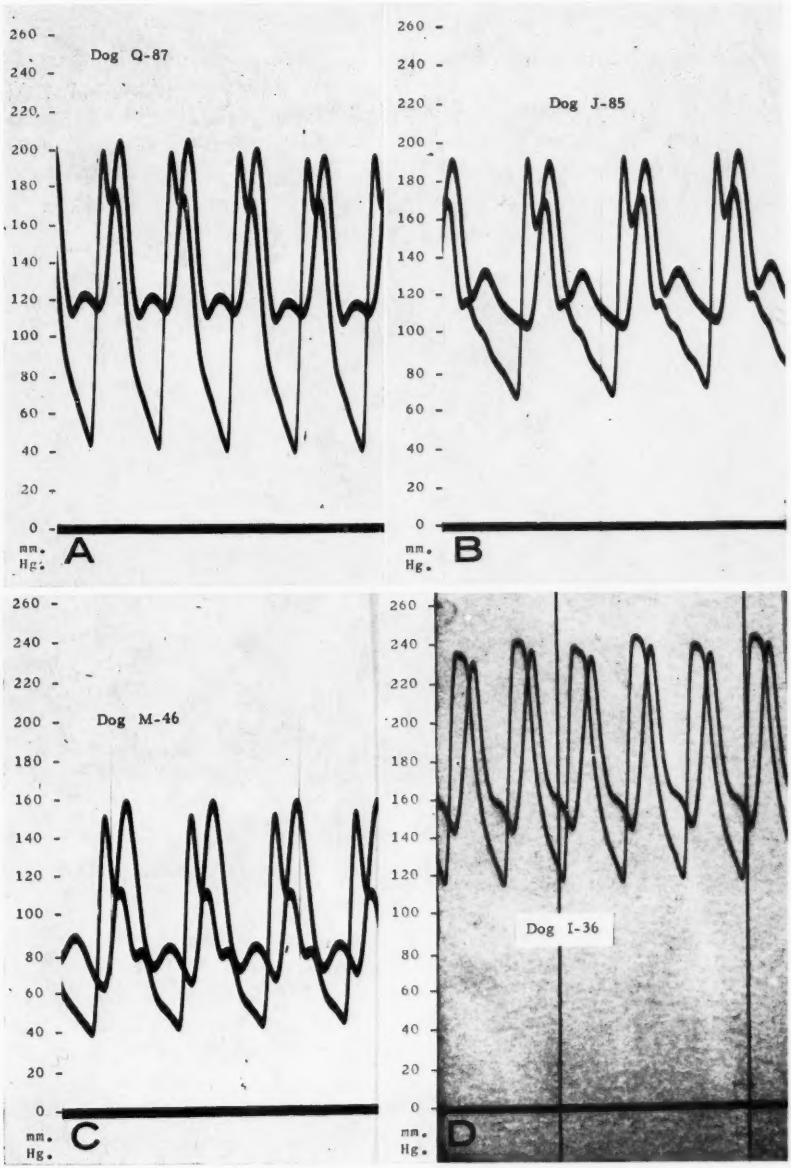

Fig. 2.—*A*, Simultaneous arterial pressure tracings proximal and distal to aortic valve homograft 3 months after operation.
B, Simultaneous arterial pressure tracings proximal and distal to aortic valve homograft 13 months after operation.
C, Simultaneous arterial pressure tracings proximal and distal to aortic valve homograft 6 months after operation.
D, Simultaneous arterial pressure tracings proximal and distal to aortic valve homograft 13 months after operation.

RESULTS

Twenty-five animals underwent this combined procedure with only four operative deaths. As previously mentioned, the first was due to hemorrhage. Another was associated with progressive heart failure following valvotomy. The other deaths were secondary to irreversible ventricular fibrillation, which occurred at the time of valvotomy. Five animals died during the first month after operation: 2 from heart failure, 2 from pulmonary complications, and 1 from empyema.

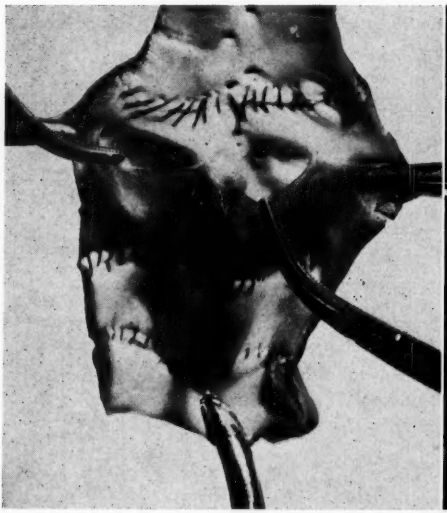

Fig. 3.

Fig. 4.

Fig. 3.—Aortic valve homograft 3 months after operation. Competence to water pressure proved at time of sacrifice.

Fig. 4.—Aortic valve homograft 13 months after operation. Cusps have become somewhat thickened but remain pliable and competent to water pressure.

Sixteen animals were available for study 1 to 13 months after operation. Five of these died from various causes during the second and third months after surgery, and 1 was killed in a fight. Seven were sacrificed at intervals up to 13 months, and 3 are still alive and well, 3, 8, and 13 months after the insertion of a homograft valve and the creation of aortic insufficiency.

In 3 animals still being followed, simultaneous pressure tracings reveal typical curves of aortic insufficiency proximal to the homograft valves with normal curves distally (Fig. 2, *A* and *B*). Similar pressure tracings were seen in 9 of the other 13 animals (Fig. 2, *C* and *D*), and competence of these homograft valves was confirmed by water pressure at the time of death or sacrifice. Examination of the cusps revealed slight thickening, but they remained pliable, and quite capable of function (Figs. 3 and 4). Microscopically valvitis with polymorphonuclear and lymphocytic infiltration was seen during the first month

Fig. 5.

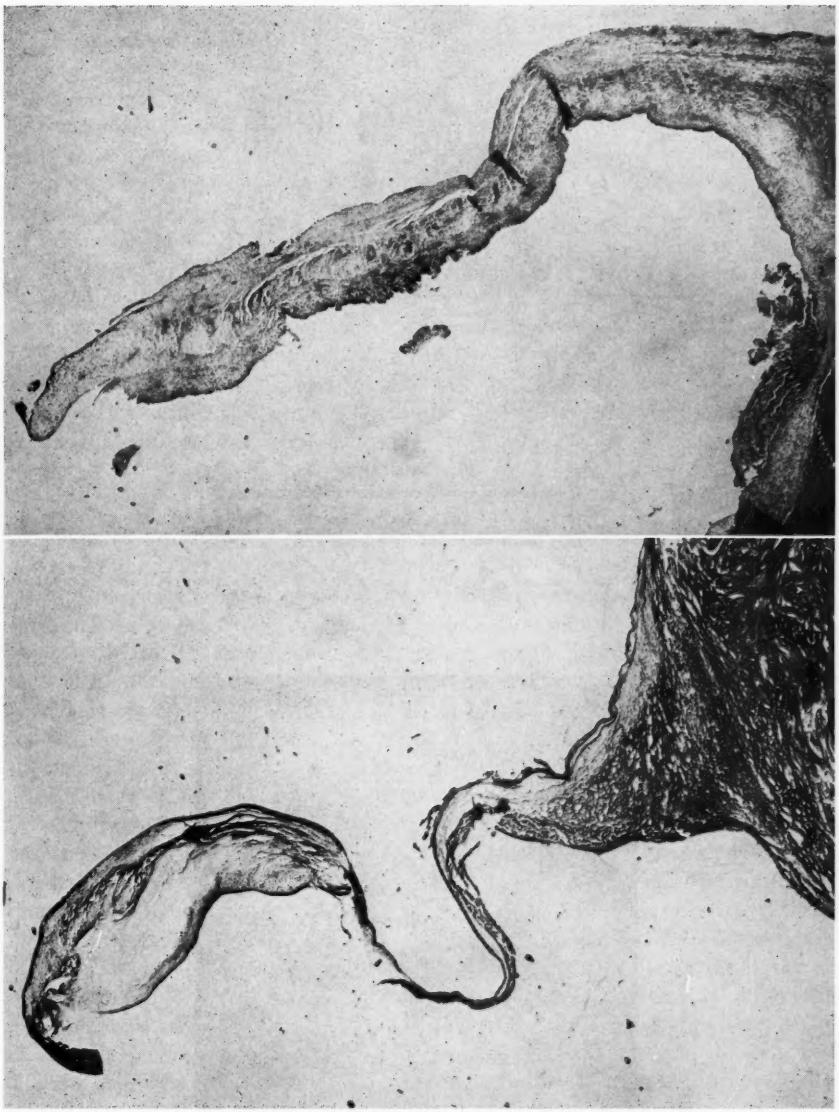

Fig. 6.

Fig. 5.—Photomicrograph of homograft cusp 1 month after operation. Minimal inflammatory response is present.

Fig. 6.—Photomicrograph of homograft cusp 13 months after operation. Cusp acellular and hyalinized with ground-glass appearance, but valve remains competent.

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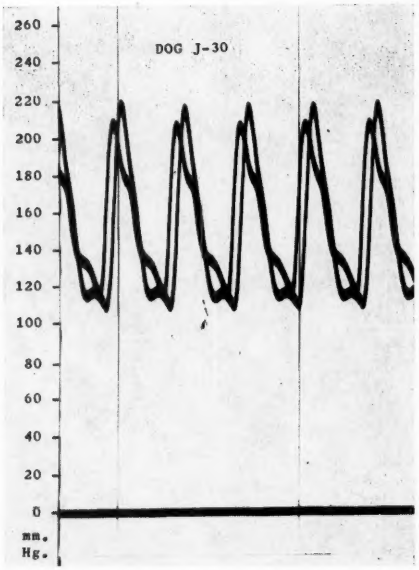

Fig. 7.—Simultaneous arterial pressure tracings proximal and distal to aortic valve homograft. Proximal and distal tracings similar throughout period of study.

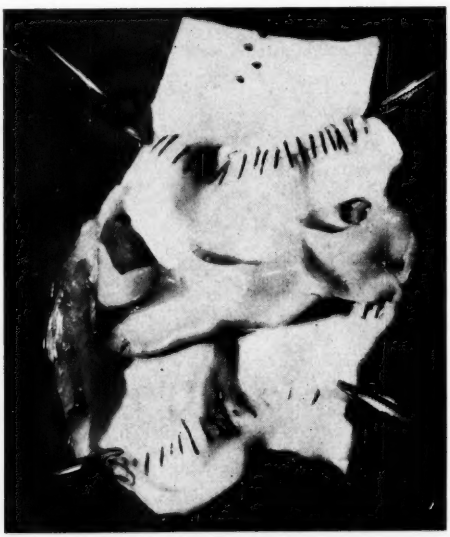

Fig. 8.—Aortic valve homograft 11 months after operation. Valve not competent to water pressure, but appears distorted at myocardial suture line.

after insertion, but was seen only rarely thereafter. Over a period of months, the cusps developed an acellular, hyalinized, ground-glass appearance (Figs. 5 and 6).

Competence could not be proved in the 4 remaining animals; in 2, pressure tracings proximal and distal to the homograft valves were similar throughout the period of study (Fig. 7). At the time of sacrifice, the homograft valves were not competent to water pressure, but the cusps were in good condition and capable of function (Fig. 8). One cannot help but speculate that these valves were distorted when the disproportionate myocardial anastomosis was made and were never competent. In the other 2 animals, marked sclerosis with shrinking of the cusps was noted at the time of death at 3½ months in 1, and at the time of sacrifice at 11 months in the other. Pressure tracings in these 2 animals revealed progressive loss of insufficiency proximal to the homograft valves, and examination of their own aortic valves suggested that the torn posterior cusp had been compensated for by the right and left coronary cusps as previously noted by Lam.[25] It would appear that loss of function in these two homograft valves was associated with the spontaneous disappearance of aortic insufficiency in the animals' own aortic valves.

DISCUSSION

Many ingenious techniques have been developed for the treatment of valvar lesions of the heart. Autogenous tissue has been used experimentally for both the atrioventricular and aortic valves.[1, 3, 6, 11, 16, 17, 30, 35, 38, 42, 44, 45] The entire pulmonic valve has been transplanted into the descending thoracic aorta.[28] In recent years numerous foreign materials have been used both experimentally and clinically in cardiac valve surgery.[2, 4, 5, 8, 9, 10, 12-15, 19-23, 27, 29, 40, 41, 43, 46, 47] Although many of these valve substitutes have shown considerable promise, none has been entirely satisfactory.

The ideal location for an aortic valve replacement would be proximal to the coronary orifices. The descending thoracic aorta was chosen for the present investigation, as this location allowed pressure tracings to be taken proximal and distal to the valves without re-opening the chest. Clinically many gratifying results have been obtained from the placement of plastic ball valves in the descending thoracic aorta.[21, 41] Until a satisfactory subcoronary valve replacement is available, it would seem advisable to continue to use the descending thoracic aorta without interfering with the function remaining in the patient's own aortic valve. This does not allow excision and replacement of a stenotic and destroyed valve, but does offer palliation to patients with aortic insufficiency until such time as the valve can be replaced in its entirety.

As with vessel homografts, valve homografts, if successful, will eventually be replaced by a more satisfactory material. Even now, the final answer in vessel grafts has not been found. No human data are included in this series, but Murray has reported clinical success with aortic valve homografts in patients with aortic insufficiency for periods up to more than 4 years.[32, 33] This type of procedure is contemplated in the near future, and should alleviate some of the

problems seen with plastic ball valves, such as noise, destruction of formed elements of the blood, emboli, and complications resulting from the insertion of a rigid tube into the pulsatile aorta.

Attempts are now being made to transplant aortic valve homografts into a subcoronary position in the dog. With technical advances made in recent years, present techniques of total cardiopulmonary bypass allow adequate exposure of the aortic valve area. Total excision and subcoronary replacement of the aortic valve awaits only the development of a satisfactory valve and a method of adequately securing it in place.

SUMMARY

Previous attempts to homotransplant aortic valves have generally met with failure, due to hemorrhage or to loss of cusp function in experiments in which no aortic insufficiency was created or the insufficiency produced spontaneously disappeared. Encouraged by occasional reports of successful cardiac valve homografts, a study was carried out in which an aortic valve homograft was inserted into the descending thoracic aorta of the dog. Aortic insufficiency was then created, and the animals were followed at intervals by pressure tracings taken proximal and distal to the homograft valves. At the time of death or sacrifice the valves were tested for competence to water pressure and examined grossly and microscopically.

Sixteen animals were studied from 1 to 13 months after operation. In 12 the homograft valves remained functional. In 2 the valves did not appear competent throughout the period of study, but the cusps remained in good condition and appeared capable of function. In 2 animals in which aortic insufficiency spontaneously disappeared, the homograft cusps underwent degenerative changes, and the valves became functionless. It would appear from these findings that homotransplantation of the aortic valve is technically feasible, and that such a valve will continue to function if a need for the valve exists.

ADDENDUM

Feb. 18, 1961. Since this experimental study was submitted for publication, aortic valve homografts have been sutured into the proximal descending thoracic aorta of 3 patients with severe aortic regurgitation. Pump bypass from the left atrium to the femoral artery was utilized during the period of aortic occlusion. These patients have shown definite clinical improvement with decrease in heart size, 7, 6, and 5 months after operation. There has been no evidence of regurgitation in any of these homograft valves.

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MYCOTIC ANEURYSM DISTAL TO COARCTATION OF THE AORTA

Report of an Unusual Case and Review of the Literature

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THE POSTDUCTAL form of coarctation of the aorta is a lesion occasionally compatible with longevity, but the great majority of patients who do not have operation die in the second and third decades of life. Progressive hypertension and congestive heart failure, cerebral hemorrhage, spontaneous rupture of the aorta, and bacterial endocarditis or aortitis have been the most common causes of death. Mycotic aneurysm formation has been rare but is usually fatal.

In 23 per cent of 104 autopsied cases of postductal coarctation reported by Reifenstein and co-workers,[1] death had been due to bacterial endocarditis and aortitis. This group had a mean survival age of 28.7 years compared to 35.0 years for the entire series. France and associates[2] demonstrated that superimposed bacterial endocarditis and aortitis are still a marked threat to life in the patient with coarctation in spite of the availability of antibiotics. While "spontaneous" aneurysms tend to form proximal to the coarctation, aneurysms secondary to bacterial infection tend to locate distal to it.[3, 4]

A review of the literature reveals 18 proved cases of mycotic aneurysm formation distal to a coarctation (see Table I). An additional case forms the basis of this report.

CASE REPORT

D. M. (U.C.L.A. 019-41-29), a 15-year-old white boy, was found to have a heart murmur at the age of 2½ years but remained well until January, 1960, when he developed a sore throat which responded in 2 days to aspirin, fluids, and saline gargles.

On Feb. 14, 1960, there developed generalized myalgia, weakness, and a fever of 102° F. Despite treatment with sulfonamides and several antibiotics over the next 2 weeks, he

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remained febrile except for a 2-day period. He was admitted to another hospital on Feb. 29, 1960, because of bilateral flank pain and hypertension.

On admission the temperature was 104° F., and weight was 81 pounds as compared to 102 pounds one month earlier. There was a basal systolic murmur, no cardiomegaly, and normal lung findings. A tender spleen was palpated three fingerbreadths below the left costal margin. There was bilateral costovertebral angle tenderness. Small splinter hemorrhages were noted in the toenail beds, petechiae were present on the skin of the lower extremities, and Osler's nodes were palpated on the plantar surfaces of several toes. Blood pressure in the arms was 145/85 mm. Hg; no recordings were made in the legs but the femoral pulses were decreased.

A chest roentgenogram on admission was entirely normal and showed no cardiomegaly or rib-notching. Four plus proteinuria and 50 to 80 red blood cells per high-power field were found. Blood cultures on March 4 and March 6 were free of growth after 2 weeks.

Subacute bacterial endocarditis, superimposed on rheumatic or congenital heart disease, with embolic glomerulitis was suspected and treatment was begun with 5 million units of intramuscular penicillin and 0.5 Gm. of oral probenecid (Benemid) daily. Complete resolution of the fever and general improvement in appetite and strength occurred within 3 days, but the microscopic hematuria, proteinuria, and the systolic murmur persisted. When the patient again began to have a daily fever of 101° F. after 14 days of treatment, he was transferred to the University of California Medical Center in Los Angeles.

At admission on March 22, 1960, his weight was still 81 pounds, but the petechiae, Osler's nodes, and splinter hemorrhages had disappeared. The spleen was now palpable only 1 cm. below the costal margin; it was firm and nontender. The patient was obviously pale and appeared chronically ill. Temperature was 103° F and pulse was 150. Blood pressures in the arms were 170/70 and in the legs 95/60 mm. Hg. The femoral pulses were delayed and weak, and a suprasternal pulsation was present. The lungs were clear, but the heart was definitely enlarged with a vigorous apical impulse in the fifth intercostal space, 2 cm. lateral to the left mid-clavicular line. There was no right ventricular heave, and no thrills were palpable. A Grade 3 harsh systolic murmur was maximal over the aortic area and radiated well to the neck vessels and down the left sternal border. There were no diastolic murmurs. The remainder of the examination was unremarkable.

Significant laboratory data included hemoglobin, 8.7 Gm.%; hematocrit, 27.5%; white blood count 17,000 per cubic millimeter with 68% neutrophils; and sedimentation rate, 25 mm. per hour. Urinalysis revealed 1+ proteinuria with 5 to 8 white cells and 20 to 30 red blood cells per high-power field. Serum electrolytes were within normal limits. Electrocardiogram demonstrated marked left ventricular hypertrophy of the diastolic overload type. Bacterial aortitis superimposed on postductal coarctation of the aorta was diagnosed. Three arterial and three venous blood cultures were drawn and the patient was started on 18 million units daily of intravenous penicillin with 1.0 Gm. of streptomycin intramuscularly twice a day. The penicillin levels were potentiated with probenecid, 0.5 Gm. daily. A circulating blood penicillin concentration on the third day of therapy was 98 units per milliliter.

On the morning after admission, a portable chest roentgenogram (Fig. 1) showed definite cardiomegaly, predominantly involving the left ventricle. A large mass with an indistinct border was noted near the base of the heart on its left border. The left costophrenic sulcus was now obliterated with a suggestion of a fluid level. Fluoroscopy revealed that the mass was intimately associated with the descending aorta and was nonpulsatile, although it moved with aortic pulsation. This was thought to represent a mycotic aneurysm distal to the coarctation. It was decided to postpone surgical intervention in an attempt to eliminate the focus of infection.

The boy remained afebrile through the first 3 hospital days. On the third day, he received one unit of packed cells. The following morning the temperature climbed to 103° F., but he was free of any other signs of infection. As the hematocrit was 30 per cent, he was given another unit of packed cells.

On the morning of the fifth hospital day, he was still mildly febrile. He had spent a restful night and had experienced no pain. Although there was no change in the cardiac outline to percussion, the heart sounds were now distant and soft. The entire left hemithorax was dull to percussion and showed definitely diminished movement with respiration as compared to the right. A roentgenogram revealed that the entire left chest was now filled with fluid. The systolic blood pressure dropped rapidly from 180 down to 120, but the pulse remained stable and the patient was alert and free of pain. Hematocrit was 23 per cent.

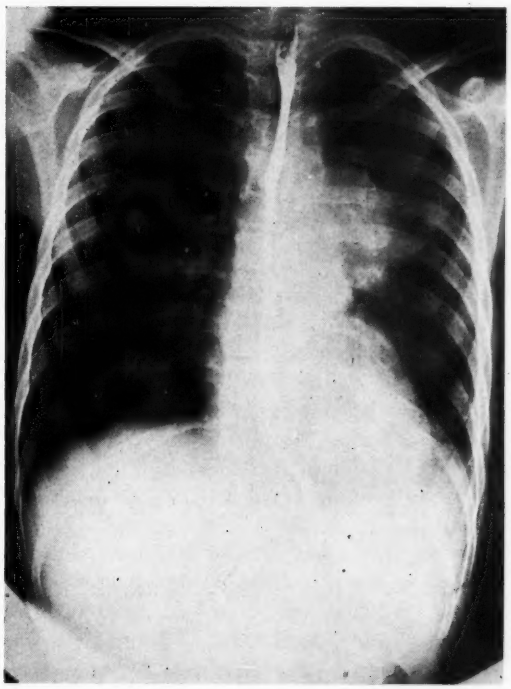

Fig. 1.

Emergency surgery was deemed necessary. Under endotracheal anesthesia, a left posterolateral thoracotomy was carried out, entering the chest through the resected bed of the fifth rib. An estimated 500 c.c. of free blood and a similar amount of clot was removed from the left pleural space. Both the left lung and a large aneurysmal mass, situated distal to a postductal coarctation, were adherent to the chest wall directly beneath the incision. In order to enter the chest and obtain adequate exposure, it was necessary to free the aneurysm from its adhesions to the chest wall. During this procedure, despite extreme caution, an exsanguinating hemorrhage ensued from the ruptured aneurysmal sac. Cross-clamping of the aorta above and below the aneurysm was ineffective in controlling the bleeding. Attempts at cardiac resuscitation were unsuccessful and the patient died.

At autopsy, the heart was enlarged and hypertrophied, weighing 390 grams. This hypertrophy was predominantly left ventricular in origin. Scarring and retraction were noted in the three-cuspid aortic valve which was thought to represent an old rheumatic process on

TABLE I. MYCOTIC ANEURYSM FORMATION DISTAL TO COARCTATION OF AORTA—NINETEEN CASES

AUTHOR	YEAR	AGE (YEARS)	CAUSE OF DEATH	ORGANISM	REMARKS
A. Unruptured Aneurysms					
1. Smith and Taggert[5]	1897	9	Pressure of aneurysm on trachea	—	—
2. Bencke[6]	1922	28	Cerebral hemorrhage	Alpha strep.	—
3. Focken[7]	1924	18	Septicemia	Alpha strep.	—
4. Kellogg and Biskind[8]	1934	16	Cardiac failure	Alpha strep.	—
5. Nicholson[9]	1940	12	Alive at time of publication	—	Untreated
6. Bauer and Iverson[10] (Case 1)	1945	20	Cardiac failure	Alpha strep.	—
7. Bauer and Iverson[10] (Case 2)	1945	22	Rupture of superior mesenteric artery aneurysm	Alpha strep.	—
8. Reifenstein, Levine, and Gross[1]	1947	28	Alive at time of publication	Alpha strep.	Treated with penicillin
B. Resected Aneurysms					
1. Sellors[11]	1956	9	Alive at time of publication	*Staph. aureus*	Treated, then resected
2. Cleland, Counihan, Goodwin, and Steiner[12]	1956	20	Alive at time of publication	Alpha strep.	Treated with penicillin, then resected
C. Ruptured Aneurysms					
1. Reifenstein[13]	1924	10	Rupture into esophagus	Pneumococcus	—
2. Smith and Hansmann[14]	1926	17	Rupture into pleural cavity	Alpha strep., nonhemolytic	—
3. Libman[15]	1929	12	Rupture into bronchus	—	—
4. Goodson[16]	1937	16	Rupture into esophagus	—	—
5. Tillich[17]	1941	17	Rupture into esophagus	—	—
6. Moragues, Moore, and Rossen[18]	1942	11	Rupture into esophagus	—	—
7. Koletsky[19]	1942	38	Rupture into pleural cavity	*Staph. albus*	—
8. France, Levin, and McNicholl[2]	1950	4	Rupture into esophagus	—	—
9. Kieffer, Linde, Kegel, and Latta	1960	15	Rupture into pleural cavity	—	Treated without eradication of infection—died at operation

gross examination. Microscopically, there was considerable chronic inflammation and scarring in this valve with several large groups of gram-positive cocci in a diplococcal arrangement, characteristic of bacterial endocarditis.

The coarctation was immediately distal to the insertion of the ligamentum arteriosus. Its lumen measured 7 mm. in diameter. Distal to the coarctation, the aorta was aneurysmally dilated. Microscopic examination revealed the wall of the aneurysm to be a relatively thin layer of fibrous tissue with signs of chronic inflammation. A similar inflammatory response was also evident in the media and adventitia of the adjacent aorta. In one place just outside the media, a small collection of neutrophils was noted which contained a few gram-positive cocci. The picture was suggestive of a septic embolus from the aortic valve to the wall of the post-stenotic aoorta. No intimal change to suggest primary bacterial infection of the intima was found. Moderate fibrosis of the adjacent pleura and lung which were adherent to the aneurysm indicated extension at an earlier time of an inflammatory process from the aorta. There was extensive infiltration of the periaortic tissues with red cells from the terminal rupture.

Additional evidence for embolization was present in the spleen and kidneys which exhibited multiple infarcts. A marked lymphoid reaction in the enlarged spleen (300 grams) was typical of cases of bacterial endocarditis.

DISCUSSION

Abbott[3] felt that a locus minoris resistentiae for invasion of organisms exists just below the stenosis where the aorta is commonly dilated and atheromatous. However, one may argue that the pre-stenotic segment of aorta is equally atheromatous and dilated. More recently Claggett, Kirklin, and Edwards[4] have noted a "jet lesion" just distal to the coarcted segment in many cases consisting of a small patch of nonatheromatous intimal thickening. They believed this "jet lesion" to be due to the localized traumatic effects of a jet-like stream of blood passing through the narrowed aortic lumen under high pressure, and, in turn, speculate that this may be followed by weakening of the underlying media so that this site becomes a locus minoris resistentiae where primary intimal invasion or secondary embolic seeding of organisms can take place. This situation is in turn favorable for subsequent aneurysm formation.

Table I summarizes the 19 proved cases of mycotic aneurysm formation distal to a coarctation of the aorta. In 6 of these patients,[5-10] death occurred from another complication. Four patients recovered from the infection with persistence of the intact aneurysm. Nicholson[9] in 1940 noted spontaneous recovery without antibacterial therapy in a 12-year-old girl. She observed progressive calcification occurring over a period of months in an aneurysmal dilation distal to the coarctation. Reifenstein, Levine, and Gross[1] described a 28-year-old man treated with penicillin in whom clinical and roentgenologic signs pointed clearly to a healed distal aneurysm.

Sellors[11] and Cleland and his associates[12] cited successful surgical excision of both the coarcted segment and the distal mycotic aneurysm with repair utilizing homologous aortic grafts after the source of infection had been eradicated with antibiotics.

Nine patients[2, 13-19] died from rupture of the aneurysm. The most common site of perforation (5 cases) was into the posterior aspect of the esophagus with

sudden exsanguination through hematemesis. The aneurysm in Libman's patient[15] ruptured into the left main-stem bronchus. The present case report is only the third recorded instance of rupture into the left pleural cavity. It differs from the previous 2 cases in the lack of pain or shock as an early sign of rupture, perhaps because the leak was small and only gradually enlarged over a period of 5 to 7 days.

In 12 of the 19 cases, blood cultures were positive. Alpha hemolytic streptococcus was cultured in 8, while nonhemolytic streptococcus, *Staphylococcus aureus, Staphylococcus albus,* and Pneumococcus were each implicated in 1 case. Negative blood cultures in the present case reflect the suppressive but obviously non-eradicative nature of the variegated and intermittent therapy during the first 2 weeks. Prompt and prolonged chemotherapy of the common bacterial infections is required in children with congenital or rheumatic heart disease if bacterial endocarditis is to be prevented. Since selection of suitable antibiotic treatment is often necessary before results of cultures are available, clinical judgment must be used in the initial choice of proper agent and adequate dosage.

The course of this patient emphasizes the importance of early definitive diagnosis and repair.[20] It is now 15 years since Crafoord and Nylin[21] and Gross[22] reported successful surgical correction of coarctation of the aorta.

Although 2 cases have been reported in recent years of surgical correction of coarctation with aneurysm after resolution of the infection, this conservative approach may be in error in some patients. In retrospect, prompt operation in this patient might have proved successful and avoided the ensuing catastrophe.

SUMMARY AND CONCLUSIONS

The formation of a mycotic aneurysm distal to a coarctation of the aorta is described in a 15-year-old boy. Eighteen cases have been reported previously, 8 terminating in rupture of the aneurysm. The present case is only the third with rupture into the pleural cavity.

The clinical course of this patient emphasizes the importance of early diagnosis and prompt correction of this congenital anomaly. In a case of coarctation with active bacterial infection and enlarging aneurysm, urgent operation may be necessary.

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CEREBRAL COMPLICATIONS OF OPEN-HEART SURGERY: FURTHER OBSERVATIONS

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THE EXPERIENCE at the State University of Iowa has been encouraging in a moderately large series of open-heart operations. A total of 394 patients have been subjected to open cardiotomies up to July 1, 1960, for various congenital or acquired diseases. Of these, 150 had correction of lesions under hypothermia alone and 244 patients with the use of the heart-lung machine. We have observed occasional cerebral complications in patients undergoing these types of operations.[3] Since there has been little reference in the surgical literature to this problem, we reviewed our records to report all such complications.

The patients frequently show no symptoms immediately after awakening from the anesthesia, even though some have had sluggishly reacting, dilated pupils and were somewhat lethargic. Localizing cerebral signs and symptoms have been observed in a few patients immediately after completion of the operation. Evidence of generalized cerebral signs appear about the second day with progressive somnolence, urinary incontinence, and often severe temperature elevation. Especially in children convulsions of the Jacksonian type followed by paralysis or weakness of the extremities have been observed. The convulsions were easily controlled by Dilantin and phenobarbital medication and the reduction of the patient's hyperthermic state to more normal levels. These alarming, but usually, self-limited complications occurred in 19 patients. Two of 150 patients operated upon under hypothermia (1.3 per cent) developed cerebral symptoms. They had closure of ostium secundum defects. Seventeen patients of 244 in whom the extracorporeal circuit was used developed postoperative cerebral signs and symptoms (6.9 per cent) (Table I). Of the latter group, 11 patients had complicated ventricular septal defects or tetralogy of Fallot. Three patients had isolated or combined mitral or aortic acquired lesions. One patient each had correction of an isolated infundibular pulmonic stenosis, an ostium primum defect, and resection of a left ventricular aneurysm.

Two patients, 1 operated upon under hypothermia and 1 using the extracorporeal circulation, experienced a delayed onset of hemiplegia 8 and 14 days

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after operation (Cases 1 and 18). Another patient operated upon under hypothermia responded poorly in the immediate postoperative period and was noted to have left hemiparesis and a positive left Babinski sign (Case 19). He recovered completely within 1 week.

TABLE I. SUMMARY OF ALL PATIENTS WITH CEREBRAL COMPLICATIONS

PATIENT	PROSTHESIS	ARREST	DURATION OF ECC (MIN.)	FLOW RATE (C.C./KG./MIN.)	CARDIAC LESION
Operative Data (Extracorporeal Circulation)					
1. D. A.	yes	yes	28	38	Tetralogy of Fallot
2. G. C.	no	no	31	52	Interventricular septal defect and pulmonary artery hypertension
3. V. B.	yes	yes	39	48	Tetralogy, cyanotic
4. D. V.	yes	yes	43	52	Tetralogy
5. D. W.	yes	yes	30	52	Tetralogy plus valvular pulmonic stenosis
6. D. D.	yes	yes	44	50	Interventricular septal defect
7. S. P.	no	yes	27	50	Interventricular septal defect with pulmonary artery hypertension
8. R. R.	yes	yes	62	48	Interventricular septal defect, infundibular and valvular pulmonic stenosis
9. P. P.	yes	yes	37	50	Interventricular septal defect, patent ductus arteriosus, pulmonary artery hypertension
10. B. H.	no	no	56	46	Infundibular pulmonic stenosis
11. D. T.	yes	no	60	50	Ostium primum
12. R. P.	yes	yes	40	64	Tetralogy, cyanotic
13. B. N.	no	no	45	68	Mitral insufficiency and stenosis, aortic insufficiency
14. D. K.	no	Intermittent	32	63	Aortic stenosis, mitral insufficiency
15. D. H.	yes	yes	42	60	Tetralogy, cyanotic
16. E. M.	no	no	49	39	Mitral insufficiency
17. L. B.	no	no	28	57	Left ventricular aneurysm

PATIENT	OCCLUSION TIME	RECTAL TEMPERATURE	DIAGNOSIS
Operative Data (Hypothermia)			
18. T. S.	6 min., 45 sec.	29.8° C.	Ostium secundum defect
19. D. P.	6 min., 30 sec.	30° C.	Ostium secundum defect

Most of the 17 patients operated upon with the use of the extracorporeal circuit responded well in the immediate postoperative period and experienced the onset of symptoms only on the first postoperative day. This led us to the conclusion that whatever the initial insult, cerebral edema played an important role. Eight had convulsions, usually Jacksonian in type. Eight, including 5 of those with convulsions, developed varying degrees of hemiparesis. Three patients were extremely lethargic but had no localizing signs. Two patients were somnolent and had some visual defects. One patient was lethargic after surgery and developed a late senile psychosis.

Three patients in this group died. Two never responded and death occurred on the third and first postoperative days (Cases 5 and 16). The other patient

(Case 13) died on the third day after operation. She was awake and well oriented during the immediate postoperative period but developed convulsions and succumbed to severe cerebral edema. The other 14 patients recovered completely from their cerebral difficulties.

In attempting to find some common factor applying to the 17 patients who had operations employing extracorporeal circulation, we encountered several pertinent facts. None of the patients had simple cardiac lesions. Seven had interventricular defects and infundibular pulmonic stenosis. Four of these were severely cyanotic. Three had ventricular defects with severe pulmonary artery hypertension, associated with a patent ductus in 1 patient. One patient had a ventricular defect requiring a large Teflon patch for closure. Three patients had mitral and/or aortic acquired disease. The remaining 3 patients had isolated muscular infundibular stenosis, a left ventricular aneurysm, and a large ostium primum defect with a cleft mitral valve.

Nine of the 11 ventricular septal defects (81 per cent) required prosthetic patches for closure and 10 of the 11 (90 per cent) required cardiac arrest. Cardiac arrest or prosthetic appliances were not employed in the patients with other lesions. The average length of the extracorporeal circulation in the 17 cases was 42 minutes.

These figures reflect the severity of the disease more effectively when compared with the average applicable figures at this institution. Up to July 1, 1960, 171 patients with ventricular septal defects and variants thereof have been operated upon. About 25 per cent of these required use of prosthetic patches and about 34 per cent necessitated cardiac arrest. The average length of the extracorporeal bypass in all patients was about 25 minutes.

Our use of the extracorporeal circulation is quite conventional. The DeWall bubble oxygenator with Sigmamotor pumps is used. The defoaming chamber is sprayed with Dow-Corning Antifoam A. The tubing is disposable. The apparatus is assembled just prior to surgery and calibrated to deliver a flow of about 50 c.c. or more of heparinized blood per kilogram of body weight per minute. The left subclavian or the common femoral arteries are used for arterial cannulization. Initially we employed filters which had been placed at the outlet of the arterial reservoir but we discarded these later on. For a period of time no filters were used in the extracorporeal circulation at all. During the last year we again are using a metal filter screen in the arterial line. The openings in the mesh of the screen measure 0.4 mm. (400 μ).

Our use of hypothermia involves immersion of the anesthetized patient in an ice bath for rapid surface cooling. The desired rectal temperature to reach at the lowest point is 30° to 32° C.

CASE REPORTS

Extracorporeal Circulation.—

CASE 1.—D. A. (53-11627), a 6-year-old boy, had a large ventricular septal defect and infundibular pulmonic stenosis. The defects were corrected with the use of a compressed Ivalon patch and potassium arrest. Extracorporeal circulation was employed for 28 minutes

at 38 c.c./Kg./min. The postoperative course was uneventful until the eighth postoperative day when he became unresponsive, with a right facial paresis, left ptosis, and bilateral Babinski signs. He recovered completely over a 2-week period.

CASE 2.—G. C. (58-4184), a 7-year-old boy, had a ventricular septal defect, complete situs inversus, and a pulmonary artery pressure of 56/19 mm. Hg. The defect was closed by direct suturing. Extracorporeal circulation lasted 31 minutes at 52 c.c./Kg./min. On the first postoperative day the boy was extremely lethargic and had a persistent deviation of his eyes to the right. He recovered completely in 10 days.

CASE 3.—V. B. (54-1775), a 9-year-old girl, had a ventricular septal defect and infundibular pulmonic stenosis with cyanosis. The defects were corrected. A compressed Ivalon patch was used on the septal defect. Potassium arrest was employed. Extracorporeal circulation was for 39 minutes at 48 c.c./Kg./min. She remained extremely somnolent for 3 days but recovered completely by the fourth postoperative day.

CASE 4.—D. V. (48-8685), a 12-year-old boy, had a ventricular septal defect and infundibular pulmonic stenosis without cyanosis. The defects were corrected. A Teflon patch was used in the septal defect. Potassium arrest was employed. Extracorporeal circulation was for 43 minutes at 52 c.c./Kg./min. On the first postoperative day he became irrational, had a left hemiparesis and a left Babinski sign. He recovered completely within 5 days.

CASE 5.—D. W. (55-11755), a 4-year-old girl, had a ventricular septal defect and infundibular and valvular pulmonic stenosis. The defects were corrected through a right ventriculotomy and pulmonary arteriotomy. A Teflon patch was used in the septal defect. Potassium arrest was employed. Extracorporeal circulation lasted 30 minutes at 52 c.c./Kg./min. Coronary air was noted at the end of the pump run but was dispersed by cardiac massage. The patient did not awaken and had a right hemiparesis. The temperature rose to 105° F. rectally. She began to have frequent convulsions, mostly on the right side. She was treated with Dilantin and barbiturates but died on the third postoperative day. Autopsy revealed marked edema of the left parietal and occipital lobes, compatible with cerebral air embolism. An undiagnosed teratoid tumor of the cerebellum was also found.

CASE 6.—D. D. (54-4371), a 4-year-old boy, had a large ventricular septal defect which was repaired with a Teflon patch. Anoxic arrest was employed. Extracorporeal circulation lasted 44 minutes at 50 c.c./Kg./min. On the first postoperative day he had frequent convulsions, coma, and left hemiparesis. He was given digitalis, Dilantin, and barbiturates. Convulsions stopped within 24 hours and at the end of 2 weeks there were no neurologic residuals.

CASE 7.—S. P. (51-11622), a 9-year-old girl, had a ventricular septal defect with a pulmonary artery pressure of 52/20 mm. Hg. The defect was repaired by direct suture and the use of potassium arrest. Extracorporeal circulation lasted 27 minutes at 50 c.c./Kg./min. On the first postoperative day she became obtunded and had a right hemiparesis. She was treated with tracheostomy. On the second and fourth postoperative days she had convulsions. There was complete recovery within 5 days.

CASE 8.—R. R. (55-7620), a 7-year-old boy, had a ventricular septal defect with infundibular and valvular pulmonic stenosis. These were repaired through ventriculotomy and pulmonary arteriotomy. A compressed Ivalon patch was used in septal defect. Potassium arrest was employed. Extracorporeal circulation lasted 62 minutes at 48 c.c./Kg./min. On the first postoperative day he became obtunded and had a right hemiparesis and bilateral Babinski signs. He was treated with tracheostomy, digitalis, and Dilantin and completely recovered within 7 days.

CASE 9.—P. P. (58-17082), a 3-year-old girl, had a ventricular septal defect and patent ductus arteriosus with pulmonary artery pressures of 82/34 mm. Hg. The defect was closed

with a Teflon patch employing potassium arrest. Extracorporeal circulation lasted 37 minutes at 50 c.c./Kg./min. On the first postoperative day she had three convulsions and was semicomatose. She was treated with digitalis, Dilantin, tracheostomy, and barbiturates and completely recovered in 2 days.

CASE 10.—B. H. (57-14109), a 30-year-old woman, had severe infundibular pulmonic stenosis without septal defect. The hypertrophied muscle was excised. Extracorporeal circulation lasted 46 minutes at 46 c.c./Kg./min. On the first postoperative day she was somnolent. On the second postoperative day she had right hemiparesis and disported herself in an irrational and rather wanton manner. She completely recovered in 1 week.

CASE 11.—D. T. (55-10316), a 23-year-old man, had a previous exploration for an ostium primum defect under hypothermia. At reoperation, closure of primum defect with a Teflon patch and repair of the cleft mitral valve was done. The extracorporeal circuit lasted 60 minutes at 55 c.c./Kg./min. The patient appeared lethargic and somewhat confused during the first 5 postoperative days. He developed paresis of the superior oblique muscle on the right eye and diplopia on the tenth postoperative day. There were some memory defects. All symptoms cleared completely over a 3-week period.

CASE 12.—R. P. (59-6081), an 11-year-old girl, had a previous Blalock operation for severe tetralogy of Fallot. Complete correction of this defect with infundibular resection and placement of a Teflon patch in the ventricular defect under potassium arrest was carried out. The extracorporeal circulation lasted 40 minutes at 64 cc./Kg./min. During the operation there was some evidence of coronary air embolization. The child developed a complete heart block and myocardial wires were placed. On the third postoperative day the child became less responsive. Weakness of the right arm and leg was noted. Some mental depression persisted for about 3 weeks. All symptoms cleared completely. The complete A-V block persisted.

CASE 13.—B. N. (58-1160), a 36-year-old woman, with known rheumatic heart disease, mitral insufficiency and stenosis and aortic insufficiency, had repair of the mitral insufficiency. The extracorporeal circulation lasted 45 minutes with a flow of 68 c.c./Kg./min. The patient was well oriented during the first 24 hours. During the second postoperative day the temperature rose to 105° F. rectally. The patient became disoriented with a marked drop of blood pressure which necessitated administration of Levophed. The patient developed generalized convulsions and died on the third postoperative day. During operation there had been considerable blood loss, probably resulting in inadequate cerebral perfusion. Postmortem examination revealed pulmonary collapse, renal tubular necrosis, acute and severe cerebral edema.

CASE 14.—D. K. (48-3965), a 39-year-old woman with calcific aortic stenosis and mitral insufficiency, had correction of both lesions. The extracorporeal circulation lasted 32 minutes with a flow of 63 c.c./Kg./min. Due to the aortic regurgitation there was much blood loss and some foaming of blood in the open left atrium during the repair of the mitral valve. The patient developed some postoperative mental confusion but no localizing signs. Recovery was complete on the sixth postoperative day.

CASE 15.—D. H. (58-10185), a 4-year-old girl, was operated upon for a severe tetralogy of Fallot. The infundibular stenosis was resected and a Teflon patch was placed in the septal defect. Anoxic cardiac arrest was employed. The extracorporeal circulation lasted 42 minutes with a flow of 60 c.c./Kg./min. The patient did not speak during the first postoperative day but was alert. On the second postoperative day, Jacksonian type of seizures involving the right side of the body were observed. The patient became stuporous. On the fifth postoperative day the child moved only the left arm and had additional convulsions. Rapid clearing of neurologic symptoms and complete recovery took place thereafter except for some weakness in the right lower extremity.

CASE 16.—E. M. (53-13169), a 34-year-old woman was operated upon for severe mitral insufficiency. The extracorporeal circuit lasted for 44 minutes with a flow of 39 c.c. per kilogram. The patient was unresponsive after operation necessitating the use of a respirator. She died 18 hours after operation. Postmortem examination revealed marked cerebral edema. Brain section showed some embolic amorphous material (? antifoam) occluding smaller arteries and producing spotty ischemia and cerebral edema.

CASE 17.—L. B. (60-5935), a 62-year-old woman, was operated upon for a large left ventricular aneurysm. On the first postoperative day the patient developed mild hypotension due to postoperative bleeding. On the fifth postoperative day the patient became lethargic and disoriented. This progressed to complete disorientation necessitating transfer to the psychiatric unit. Complete recovery took place after several weeks. Impression: Postoperative senile psychosis.

Hypothermia.—

CASE 18.—T. S. (43-7186), a 27-year-old woman, had the repair of an atrial ostium secundum defect. Occlusion lasted 6 minutes and 45 seconds at 29.8° C. Two weeks postoperatively she developed a right hemiparesis coincident with episodic atrial fibrillation. The arrhythmia was treated effectively. When next seen 5 months later she had recovered completely.

CASE 19.—D. P. (57-7013), a 17-year-old boy, had the repair of an ostium secundum defect. Occlusion lasted 6 minutes and 30 seconds at 30° C. (rectally). On the operative day he was difficult to arouse. He had a hemiparesis and a left Babinski sign. Recovery was gradual and complete within 1 week.

DISCUSSION

The causes of most of the cerebral complications remain obscure. In two instances clot embolism originating from the left side of the septal suture line could be the cause for the delayed sudden cerebral symptoms 1 week and 2 weeks postoperatively (Cases 1 and 18). Air embolism may be the cause for complication in the remaining patient who was operated upon using hypothermia (Case 19). Air embolism also cannot be excluded in any of the other patients operated upon with the use of the heart-lung apparatus if septal defects existed during right cardiotomies or if the left side of the heart or the aorta was opened to carry out the contemplated repairs. In 1 patient (Case 10) with isolated infundibular muscular stenosis, embolization of air could not be the cause for the cerebral symptoms inasmuch as no septal defects existed. However, we did not use a filter in the extracorporeal circuit in this instance.

Some of the physiologic changes occurring during the course of extracorporeal circulation have been investigated and are well documented.[1, 2, 4-7, 9] It is improbable that acidosis or hemoglobinemia[1, 2, 7] play important roles in what we have called for the sake of brevity, rather than accuracy, "the pump syndrome." Hypoglycemia[5] as a result of dropping glucose levels in stored blood is not a possibility since our heparinized blood is drawn within 2 to 4 hours of operation.

The possible role of antifoam embolization has been investigated[9] and undoubtedly can produce a picture similar to the one described. Much larger amounts of the substance, however, than used in patients have to be introduced

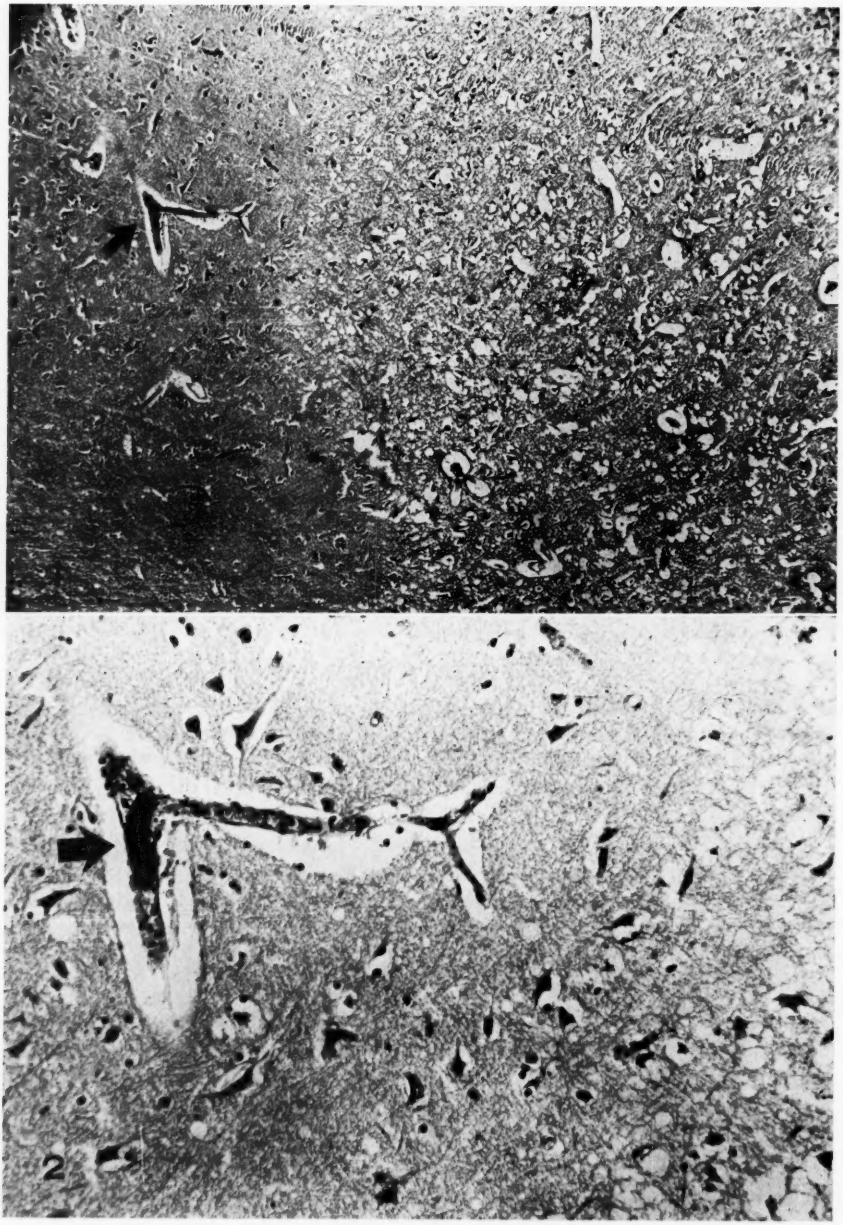

Fig. 1.—Brain section (Case 16) which shows marked cerebral edema and piece of foreign material (? antifoam) in small cerebral artery.

Fig. 2.—Photomicrograph of small cerebral vessel (Case 16) with amorphous foreign material (? antifoam) obstructing the lumen.

into the cerebral circulation of experimental animals to produce changes in the brain. We are in no position to compare the amount of antifoam washed into the patient by the pump with the amount needed to produce cerebral findings. Smears made from the filter deposits showed only minimal amounts of material which could be stained by fat stains (oil red 0) and it could not be identified definitely as antifoam substance. In the brain of 1 of the patients (Case 16) who died, amorphorus embolic material in the smaller vessels was found which may be antifoam substance (Figs. 1 and 2).

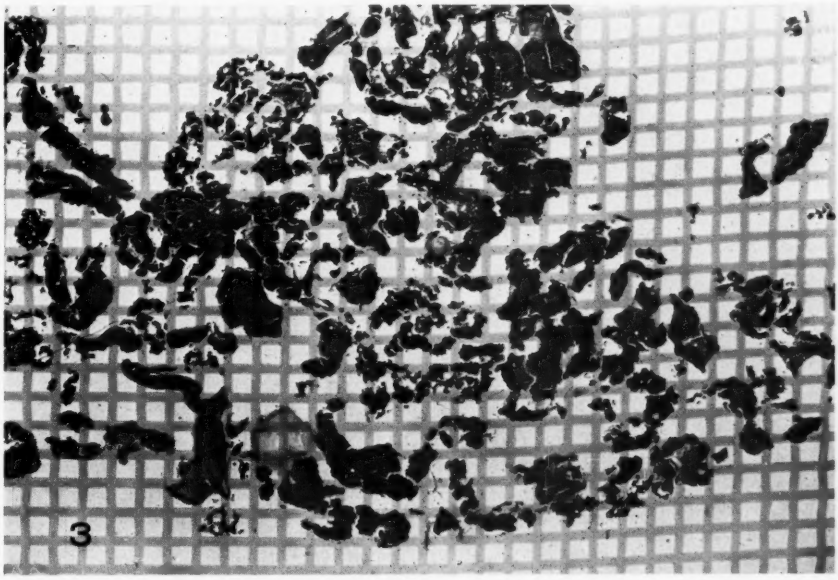

Fig. 3.—Tissue and fibrin debris from filter compared with size of filter (mesh openings 400 μ).

The embolization of fibrin clots seems somewhat remote as a cause in view of what certainly should be an adequate dose of heparin (1.5 mg./Kg. body weight) given a few minutes before the vessels are cannulated. Nevertheless, some fibrin material did collect on the filters whenever they were used, particularly during prolonged pump runs. It is therefore a possible cause of embolization in case filters are not used or if the fragments are small enough to be pushed through the filter mesh (Fig. 3).

As mentioned previously, we have operated upon many patients without the use of filters and with no difficulty whatsoever. To our surprise, after we started the use of filters again, we did find the presence of larger and smaller pieces of tissue on the filter surface in nearly all patients who had resection of myocardial muscle during the repair of their defects. These fragments were aspirated by the coronary suction system into the extracorporeal circuit (Fig. 4). In 1 patient (Case 17) with a left ventricular aneurysm, organizing thrombus,

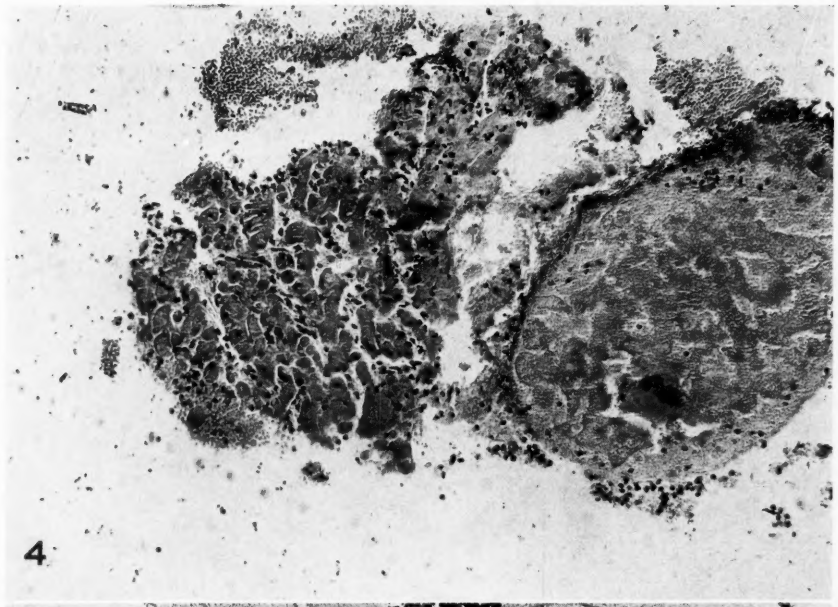

Fig. 4.—Myocardial muscle obtained from screen deposit in a patient who had resection of muscle during repair of a tetralogy of Fallot.

Fig. 5.—Tissue debris obtained from filter in a patient with a left myocardial aneurysm (Case 17).

connective tissue and even cartilage fragments were found in the microscopic sections obtained from the filter deposit (Fig. 5). No such tissue debris was found in patients who did have repair of simple defects or for valvular disease of one type or another. It stands to reason that smaller fragments may have been pushed through the filter screen into the arterial side of the patient, possibly being the cause of some cerebral symptoms. This could possibly be obviated by insertion of an additional filter screen in the coronary suction line.

Arterial air embolism can occur in several ways during extracorporeal circulation. Air may be retained in the left side of the heart or aorta after defects have been closed and carried peripherally when normal circulation is resumed (Fig. 6). We have occasionally lowered the patient's head and occluded the

Fig. 6.—Photomicrograph which shows severe cerebral edema in Case 5. Lesions probably were due to localized air embolization.

innominate and left carotid arteries for about 60 to 90 seconds when the heart is restarted after cardiac arrest to prevent trapped air from reaching the brain. This was done in 2 patients (Cases 8 and 9) who nevertheless developed cerebral signs. Another situation leading to systemic air embolism is present in patients with unrecognized interatrial septal defects or probe-patent foramen ovale in association with interventricular lesions. If the ventricular defect is closed first and the atrial last, entrance of air into the left side of the heart through the atrial defect is likely due to the sucking action of the left ventricle during diastole in a beating heart.

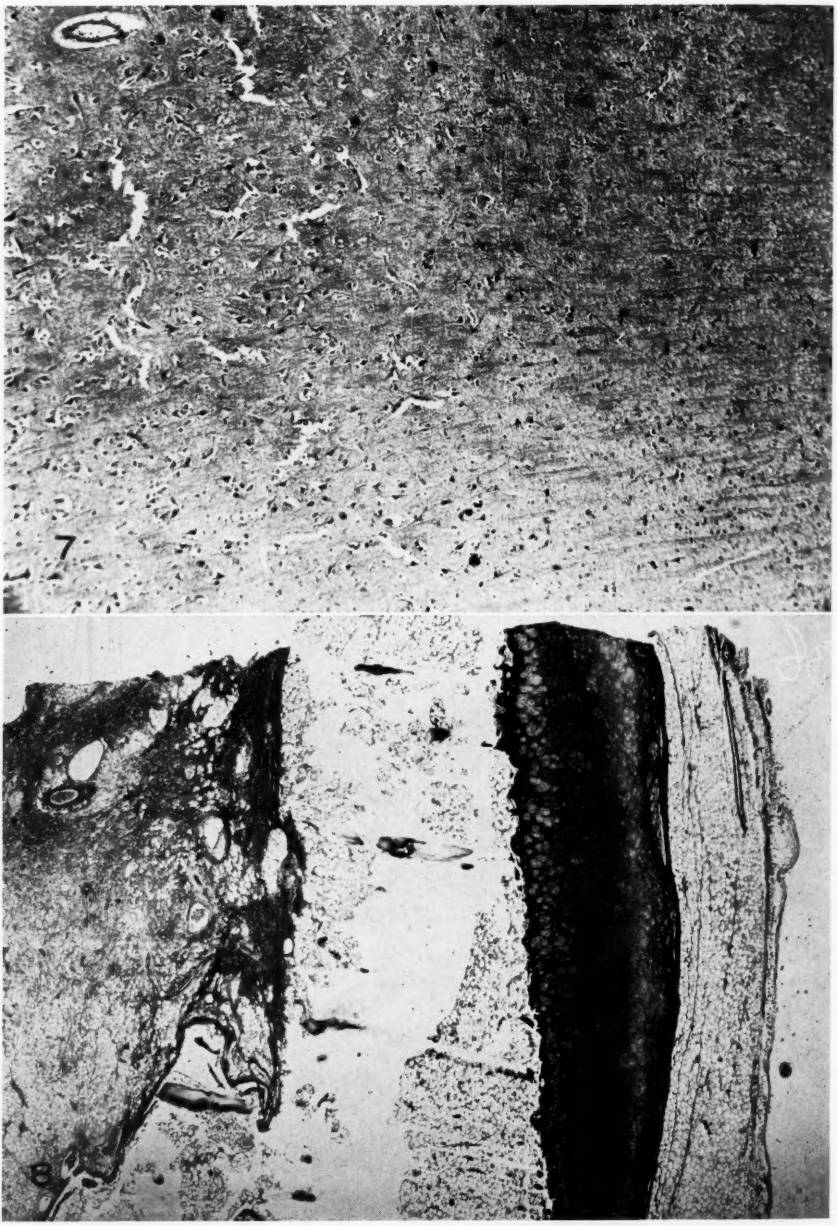

Fig. 7.—Brain section which shows severe cerebral edema (Case 13). No foreign material was found in cerebral vessels. Lesion was probably caused by inadequate cerebral perfusion.

Fig. 8.—Photomicrograph of the teratoid cerebellar tumor found at autopsy in Case 5.

Small air bubbles could enter the systemic circulation from the oxygenator. This would involve passage of air through the defoaming chamber, the helix, the reservoir, and the screen bubble trap, an imposing series of obstacles.[11]

The third possibility involves the release of oxygen bubbles from formerly cooled hypersaturated blood which becomes warm upon entering the patient.[2, 4]

Interruption of a dominant vertebral artery during freeing of the left subclavian artery as suggested by Thomas and co-workers[10] is not a probable cause of these complications in view of the fact that the vertebral artery is not ligated and some of the patients had findings suggestive of right-sided brain damage. Furthermore, in our patients the clinical signs and histopathologic changes indicated distribution in the cerebral hemispheres rather than in the distribution of the vertebral-basilar system.

We could not find definite correlation in our patients of abnormal electroencephalographic tracings taken during the pump runs and the development of postoperative cerebral signs. Temporary abnormal electroencephalographic tracings just before starting the pump runs but after cannulation of the superior vena cava have been seen occasionally.[8] The same has been observed during the short time span just after stopping the extracorporeal circuit and before the heart has taken over its action effectively. At times, abnormal electroencephalographic patterns have been seen during the pump runs without any postoperative cerebral complications.

The causes producing cerebral complications in the reported patients can only be speculated upon; probably several causes are at work. The best possibilities, however, seem to be air embolization due to trapped air in the left side of the circulation or, if myocardial tissue was resected, embolization of this material into the cerebral circulation if no filters are used. The passage of smaller fragments, fibrin, and antifoam substance through the filter screen undoubtedly can be a cause. More definite deductions can be made in 3 patients who succumbed to their cerebral difficulties and in whom examination of the brain was carried out. Prolonged inadequate body and cerebral perfusion due to severe blood loss during the cardiac bypass may have been the difficulty in some patients and caused the death from cerebral anoxia and resulting cerebral edema in 1 (Case 13) (Fig. 7). The possibility of antifoam embolization as a cause of symptoms in the reported patients warrants further investigation, especially in view of the findings in the brain sections in 1 patient (Case 16). An unsuspected cerebellar teratoid tumor in the brain of 1 patient (Case 5) cannot be given as the cause of her symptoms and death (Fig. 8). Coronary air embolization had been noticed during operation and there were localizing cerebral symptoms. Examination of the brain showed cerebral edema and ischemia of the left occipitoparietal area, consistent with localized air embolization.

SUMMARY

Nineteen patients with cerebral complications after open-heart surgery have been presented. Hypothermia alone was used in 2 patients and the heart-lung

apparatus in 17. These complications resulted in death in 3 patients. Multiple factors which may cause cerebral difficulties have been discussed but they must be regarded as purely speculative in the group of surviving patients. The causes leading to the death of the 3 patients are given and documented in part by the histopathologic findings. They were cerebral edema caused by cerebral anoxia due to inadequate cerebral perfusion, air embolization, and, probably, embolization of antifoam substance.

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TREATMENT OF CARCINOMA OF THE BRONCHUS BY INTERSTITIAL IRRADIATION

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IN SPITE of all the efforts made to diagnose lung cancer earlier, only 20 per cent of patients suffering from this disease are considered worthy of surgical exploration. In this small group perhaps 1 patient in 5 will have an irremovable tumor. For the vast majority of patients, therefore, radical surgery is impracticable and irradiation remains the only alternative means of radical treatment. In an attempt to improve the effectiveness of irradiation a method has been developed whereby radioactive material is inserted into the tumor at the time of operation. For some years the isotope of gold (Au^{198}) had been used in the form of local implants in the treatment of cancer in the skin, stomach, and bladder, and other sites. The technical aspects of its administration had been described by Hodt, Sinclair, and Smithers[1] in 1952. In 1958, Henschke[2] reported the application of interstitial irradiation in primary bronchial carcinoma.

Our first patients were treated with radioactive gold in January, 1955, and between then and June, 1959, 100 patients have received some form of interstitial irradiation. This is only a small group which cannot be analyzed easily or comprehensively; but it provides a guide or pointer which we believe justifies further use and extension of the method.

APPARATUS

Interstitial irradiation implies the permanent or temporary implantation of radioactive sources. Ormerod[3] has had considerable experience with the permanent implantation of radon seeds, whilst Tudor Edwards[4] effectively employed temporary implants in the bronchus. Smithers,[5] however, considers that radioactive gold grains are more suitable for the following reasons. The accurate dimensions of the grains allow them to be loaded into magazines and used in a specially designed "gun." Radon seeds, by contrast, vary in size and must therefore be planted singly. The total implant can be performed more quickly and with greater accuracy with gold grains and with less exposure to the operator. Gold grains are premanufactured before being made radio-

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active. If unused, they may be reactivated in the pile, whereas radon seeds are wasted; but, for small numbers, there is little difference in cost. Finally, protection is easier for Au^{198} than for radon.

The grains consist of cylinders of gold encased in platinum. They are accurately manufactured, the over-all dimensions being 2.5 mm. long and 0.8 mm. in diameter. When irradiated with neutrons in a nuclear reactor, the isotope of gold, Au^{198}, is produced. This nuclide emits both gamma and beta rays, but the latter are partially filtered off by the thin casing of platinum to reduce them to a level similar to that of radon seeds, thus avoiding necrosis of tissue close to the source. The half-life of Au^{198} is 2.7 days, and it is usual to specify the total activity in terms of millicurie equivalents of radon for convenience in using the radon tables. As a rule, gold grains equivalent to 1 millicurie of radon at the time of implantation are employed.

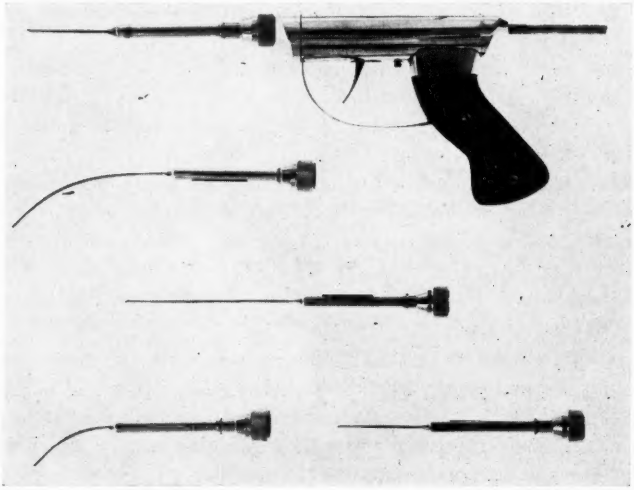

Fig. 1.—Photograph of introducer or "gun," showing the various types of needle available.

The gold grain introducer was designed at the Royal Marsden Hospital (Hodt, Sinclair, and Smithers, 1952)[1] (Fig. 1).* The aluminum magazine, containing fifteen radioactive gold grains, is loaded into the barrel, which is then screwed onto the stock. Activity has been measured prior to using the grains. The gun is primed by pushing home the shaft. The grains then rest in the end of the needle, and one grain is ejected each time the trigger is pulled, and this event is recorded on the top of the gun. The needle may be straight or curved and is graduated in centimeters. A longer needle is available for bronchoscopic implantation.

INDICATIONS

Group A.—Growth not resectable at thoracotomy: The growth may be found to be more extensive than anticipated and may be found to have in-

*Manufactured by the Medical Supply Association, Ltd., 95 Wimpole St., London, W. 1.

vaded a vital organ, such as the trachea, aorta, or heart, or there may be widespread invasion of the mediastinum or chest wall. Such lesions cannot be safely excised and constitute a good indication for interstitial irradiation. Fifty-six of our patients belong to this category.

Group B.—Growth resectable but respiratory reserve inadequate for radical excision: The respiratory reserve of any individual patient will often determine the amount of lung tissue which can safely be removed. It is sometimes discovered at thoracotomy that the effective removal of the tumor would remove more lung tissue than could safely be spared and would subject the patient to the risks of becoming a respiratory cripple. In such cases, interstitial irradiation may be employed as a reasonable alternative.

Occasionally, peripheral tumors are encountered in patients who would not survive the loss of any lung tissue at all, but in whom the absence of a definite diagnosis precludes conventional radiotherapy. In such patients, thoracotomy with biopsy and the preparation of a frozen section is performed. If the pathologist diagnoses cancer, interstitial irradiation is well justified.

There were 5 patients who fell into one or other of the above categories, and at the time of thoracotomy were treated by implantation of gold grains.

Group C.—Supplementary to resection: There are occasions when it is not possible to remove all the growth with certainty—for instance, in the case of a peripheral tumor attached to or invading the chest wall, or with extension of a tumor into the mediastinum or diaphragm, or with the involvement of mediastinal nodes. In a special category is the apical lung tumor—the so-called Pancoast syndrome—which invades ribs and vertebral bodies as well as the brachial plexus and sympathetic chain. Resection of such tumors is usually palliative but desirable if only to relieve the severe pain which is so often a feature of this syndrome. In such cases we have been implanting the bed of the resected tumor with gold grains.

Eighteen patients had an implant performed in addition to the resection of all macroscopic tumor.

Group D.—Growth inoperable but accessible for endobronchial implantation: Bronchoscopy may show a tumor within the lumen of the bronchus but extending to involve the carina or the wall of the trachea and thus exceeding the limits of surgical excision. In such a case, implantation may be performed through the bronchoscope. This treatment may also be used in patients who have an endobronchial tumor visible bronchoscopically but who would not tolerate resection of that amount of lung indicated by the bronchoscopic findings. This method is also useful in dealing with local endobronchial recurrence after resection at an earlier stage.

Twenty-one patients received an implant of radioactive gold grains through the bronchoscope.

ASSESSMENT OF DOSAGE

In this group of patients, a tumor dose of 6,000 rads has been aimed at as a convenient starting point following the rules formulated by Paterson

and Parker[7] in 1934. These rules have determined the number of grains needed for planar implants, and the distribution for both planar and spherical implants. The number of grains necessary for volume implants is derived from the rules laid down by Shalek and his associates[8] in 1957. The number and distribution of gold grains depend on the geometry and size of the lesion, and on the strength of the grains.

The distribution may be briefly summarized as follows. A tumor mass less than 1.5 cm. thick is assumed to be a plane and is treated as a circle. If the diameter of the lesion is less than 5 cm. then two thirds of the grains are implanted evenly around the periphery, and the remaining third is distributed in the center. When the lesion is more than 5 cm. in diameter, the grains are evenly distributed between the center and the periphery.

If the lesion is thicker than 1.5 cm. it is treated as a sphere. Three quarters of the grains are then placed in the periphery—the "shell" of the sphere—and the remaining one quarter in the center—the "core."

This scheme, although rather simplified, is perfectly adequate to obtain a reasonable implant, and is easily understood and performed. It is available in tabular form in the operating room, calibrated for grains which are one millicurie equivalent and can be referred to after the tumor size has been assessed (Table I).

TABLE I. DISTRIBUTION OF GOLD GRAINS REQUIRED TO GIVE 6,000 RADS TO CIRCULAR OR SPHERICAL IMPLANTS*

DIAMETER (CM.)	NO. OF 1 MC. RADON EQUIVALENT GRAINS	DISTRIBUTION OF GRAINS
Planes		
1.	3	
2.	6	
3.	9	⅔ peripherally
4.	12	⅓ central area
5.	16	
6.	21	½ peripherally
7.	26	½ central area
Spheres		
1.	2	
2.	6	
3.	11	
4.	18	¾ in shell
5.	26	¼ in core
7.5	43	
10.	100	

*Lesions in the form of a slab less than 1.5 cm. thick should be treated as planar (circular) implants.

Nevertheless, it is very difficult even with long experience to obtain an implant which conforms completely to the Paterson-Parker rules. Moreover, as the implantation of discrete sources does not produce uniform irradiation of a tumor volume, the problem of radiation dose is more complex than for external irradiation. The dose is very high—many thousands of rads—at the "maximum," close to the source, and is much lower at the "minimum," at a

distance from each source. In the present series a good implant is defined as one in which the minimum tumor dose is about 6,000 rads. This is probably rather lower than is desirable for the best results.

The dose delivered to the lesion by the implant is measured as soon as possible after thoracotomy, by means of double-shift radiographs.

INTERSTITIAL IRRADIATION COMPARED WITH EXTERNAL IRRADIATION

A gold grain implant can give a high tumor dose with a smaller integral dose than is possible with external irradiation even though a large implant may give a considerable integral dose. A smaller proportion of the body is irradiated and there is greater sparing of the normal tissues, the skin being completely spared. There are, therefore, fewer side effects and the patient may complain only of nausea and slight dysphagia for the first day or two. Indeed, the side effects are little more than would be expected after any thoracotomy. Long-term effects, which may occur after external irradiation, such as dyspnea from pulmonary fibrosis, have not been encountered after gold grain implants. Furthermore, at thoracotomy, the growth can be seen and felt, and it is easier to assess its size than by studying radiologic abnormalities. Normal lung tissue and uninvolved lymphatics are not unnecessarily irradiated, as may happen with external irradiation. The latter will deliver homogeneous irradiation to whatever volume is assumed to be tumor. Unfortunately this volume, based on clinical, radiologic and bronchoscopic findings, and often without the advantage of thoracotomy, may, even with considerable experience, be woefully inaccurate.

The time in hospital after a gold grain implant is no more than that required for most patients who have had a thoracotomy. This period, of about 3 weeks, is about half that required for a full course of external irradiation.

It is very important to the patient to find that he has not had a thoracotomy for nothing. He can be assured that he has had worth-while treatment at the operation, and his case is not necessarily hopeless.

In some patients very speedy palliation of pain or of stridor due to an endobronchial tumor may be obtained long before external irradiation could be used or become effective.

RESULTS OF TREATMENT

Between January, 1955, and June 1959, at the Brompton and King's College Hospitals, 100 patients had been treated with gold grain implants for carcinoma of the bronchus. All these patients have been followed for at least 6 months.

Survival.—Five patients died soon after operation. Four of the patients had thoracotomy and implantation alone; the fifth patient had grains implanted in addition to resection of the lesion. There were, therefore, four deaths in a group of 61 patients who had a thoracotomy and implantation as the only treatment, and this is equivalent to an operative mortality of 7 per

cent. One patient died of heart failure, and another of peripheral circulatory collapse on the night of the operation. A third patient died of pneumonia and another of respiratory failure. The fifth patient died of a tumor embolus at the time of operation.

Seventy-six patients have subsequently died from progression or recurrence of the original tumor.

Nineteen patients are alive, and the length of survival extends over a period from 5 to 51 months. Fifteen of this group are perfectly fit, but 4 are known to have recurrence.

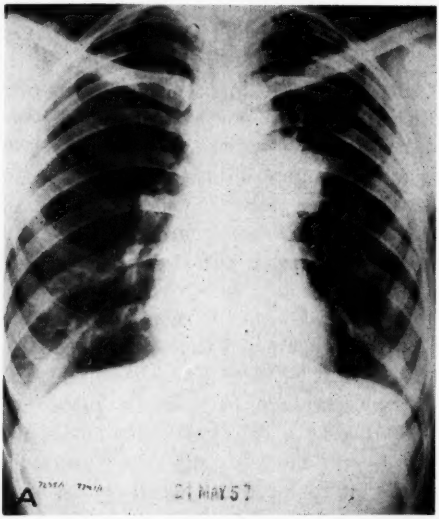

Fig. 2.—*A*, Posteroanterior radiograph of woman, aged 32. Thoracotomy revealed extensive mediastinal involvement with undifferentiated carcinoma, which could not be removed.

All 61 patients who had radioactive sources implanted at thoracotomy without resection have been observed for a minimum period of 6 months; 27 (44 per cent) died during that period. The survival rates estimated by the life-table method were 56 per cent at 6 months, 25 per cent at 1 year, and 14 per cent at 2 years (Table II). The tumor was reported of squamous type in 19 and the 1-year survival rate was 38 per cent. For the 27 with undifferentiated tmors, the corresponding rate was 17 per cent.

Twenty-one had intrabronchial insertion of radioactive sources. Only 8 (38 per cent) survived 6 months. Eighteen had a resection as well as interstitial irradiation. The estimated 1-year survival rate was 35 per cent.

Of the entire group of 100 patients, 53 per cent survived 6 months and the estimated survival rates at 1 year and 2 years were 23 per cent and 13 per cent.

Comparison of Survival With a Series Not Having Interstitial Irradiation.—In a group of 101 who had a thoracotomy without resection between 1951 and 1958 and whose cases were registered by the Joint Consultation

Clinic of the Brompton and Royal Marsden Hospitals, the estimated survival rates were lower than the present group treated by interstitial irradiation (Table III). The rates were also lower in both histologic types. On the other hand, the survival rates in a group of 47 patients who had high voltage radiotherapy directed to the primary tumor and/or the mediastinum after thoracotomy were higher.

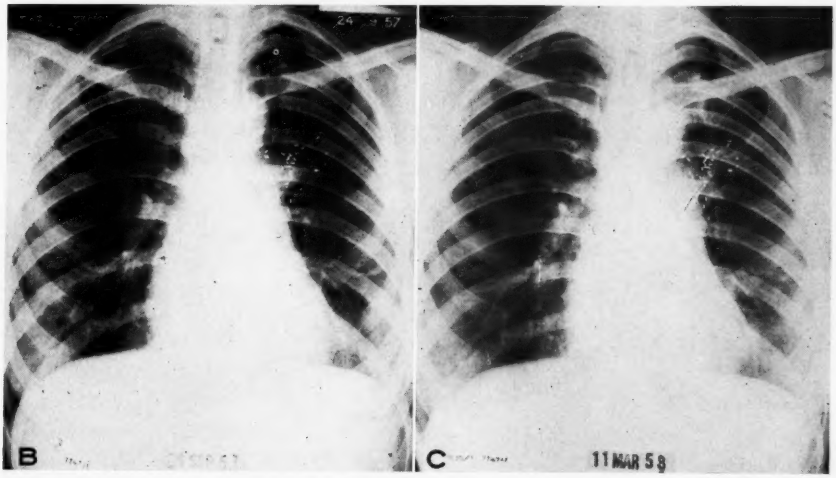

Fig. 2.—Cont'd. *B*, Four months after interstitial irradiation: the radiograph is almost normal. *C*, Three months later and there is still no deterioration.

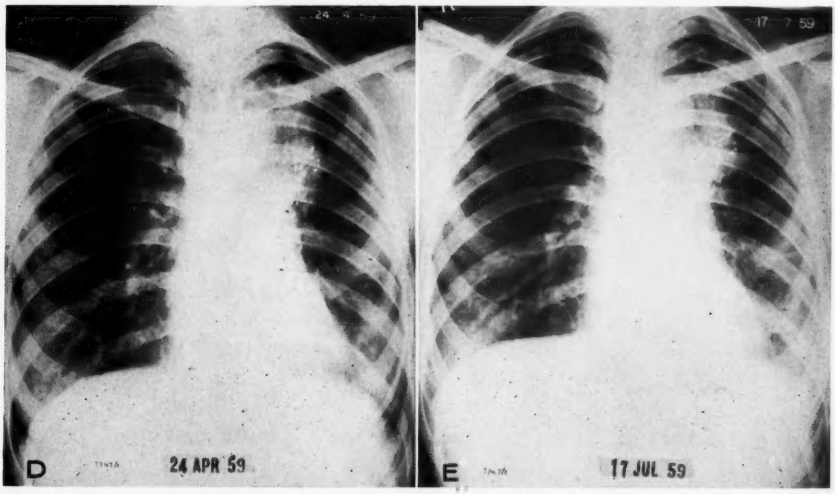

Fig. 2.—Cont'd. *D*, Eighteen months after implantation—reappearance of shadow in the left hilum, but patient is asymptomatic. *E*, Twenty-one months after implantation—shadow in left hilum is no larger, patient is still asymptomatic and it is suggested that shadowing is due to fibrosis.

These comparisons are, however, inaccurate. Some patients may have been selected for radiotherapy by either method because of the limited extent of the disease, even though the tumor was not removable because of its situation. In fact, both radiotherapy groups could have fared better merely because they contained fewer patients with extensive lesions. Moreover, those treated by high-voltage therapy included, of course, none who died within a few weeks of the operation. Of the 61 patients treated by interstitial irradiation, 4 died within a month. If these are excluded, the 6-month survival rate becomes 60 per cent and the year rate 26 per cent.

The entire group of 148 in the Brompton and Royal Marsden Hospitals' series had rates of 48 per cent at 6 months and 13 per cent and 2 per cent at 1 and 2 years compared with 56 per cent, 25 per cent, and 14 per cent, respectively, for the interstitial irradiation group. But a more meaningful

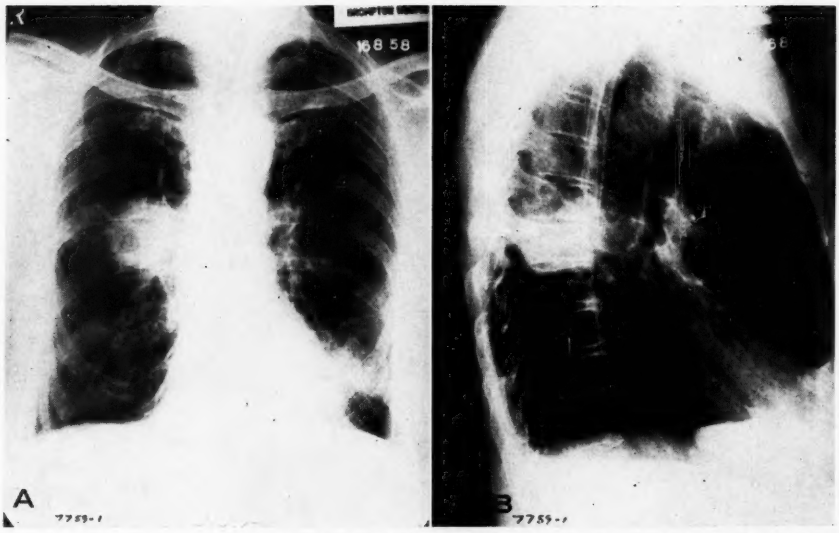

Fig. 3.—*A* and *B*, Posteroanterior and lateral radiographs of man aged 72, showing lesion in apex of right lower lobe which was a carcinoma. Interstitial irradiation performed as patient would not tolerate resection of any lung.

comparison would be between the former group and a group including both those treated by interstitial irradiation and those operated upon during the same period and considered to have lesions too extensive for such treatment.

It seems reasonable to conclude that the patients treated by thoracotomy and interstitial irradiation fared no worse than those treated by thoracotomy only and they may have fared better, but there is no satisfactory evidence that they did better than those treated by high-voltage therapy after thoracotomy.

Relief of Symptoms.—In treating a patient who is suffering from cancer, we are concerned not only with the problem of eradicating the growth. Indeed, much more often we are required to relieve his symptoms, and thereby

make life more tolerable for him. There were 72 patients suffering from symptoms directly attributable to carcinoma of the bronchus, who were given a radioactive gold grain implant as the only definite form of treatment. Fifty of these patients, or just over two thirds, had complete remission of

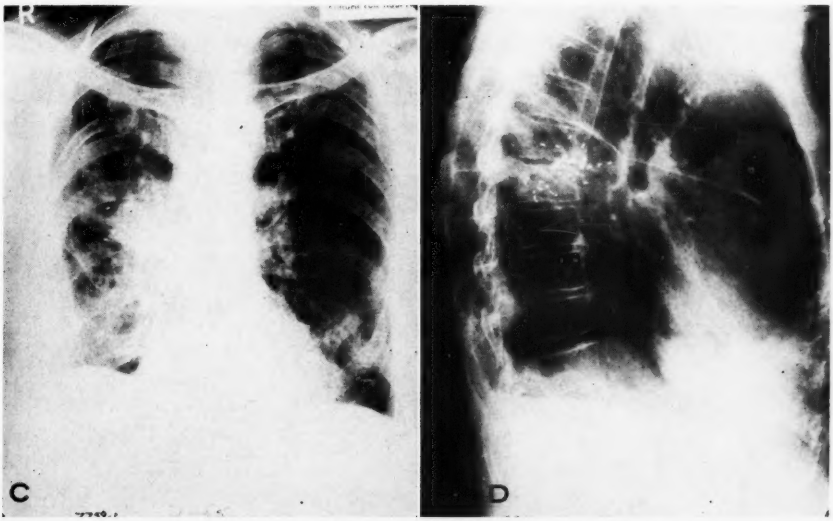

Fig. 3.—Cont'd. *C* and *D*, Posteroanterior and lateral radiographs made 3 weeks after implantation.

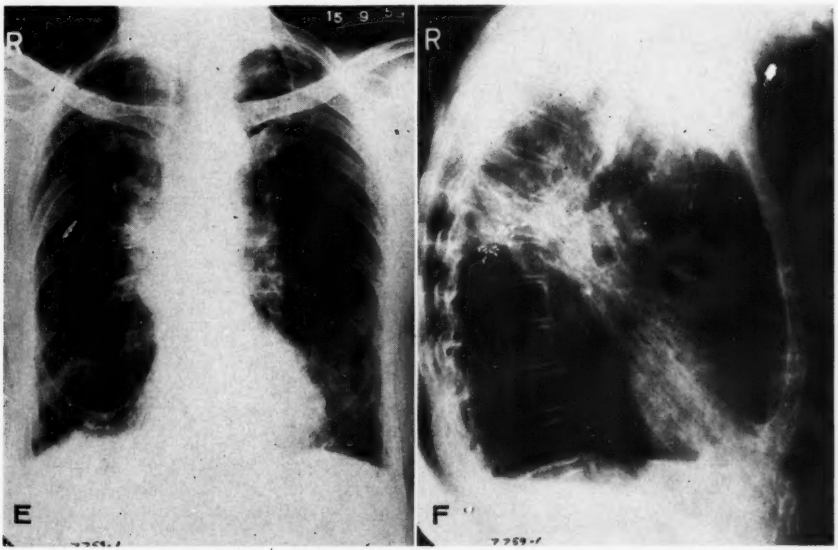

Fig. 3.—Cont'd. *E* and *F*, Similar films taken 13 months after operation. The lesion is much smaller, and this is also shown by the crowding together of the grains.

TABLE II. SURVIVAL RATES OF 100 PATIENTS WHO HAD A THORACOTOMY WITH OR WITHOUT RESECTION, AND INTERSTITIAL IRRADIATION, OR INTRABRONCHIAL IRRADIATION

	TOTAL PATIENTS IN GROUP	SURVIVAL RATES (LIFE-TABLE METHOD) (%)		
		6 MO.	1 YR.	2 YR.
Interstitial irradiation at thoracotomy, without resection	61	56	25	14
Squamous	19	67	38	–
Undifferentiated	27	52	17	–
Type unknown	15	–	–	–
Resection plus interstitial irradiation	18	60	35	–
Intrabronchial irradiation	21	38	9	–
Totals	100	53	23	13

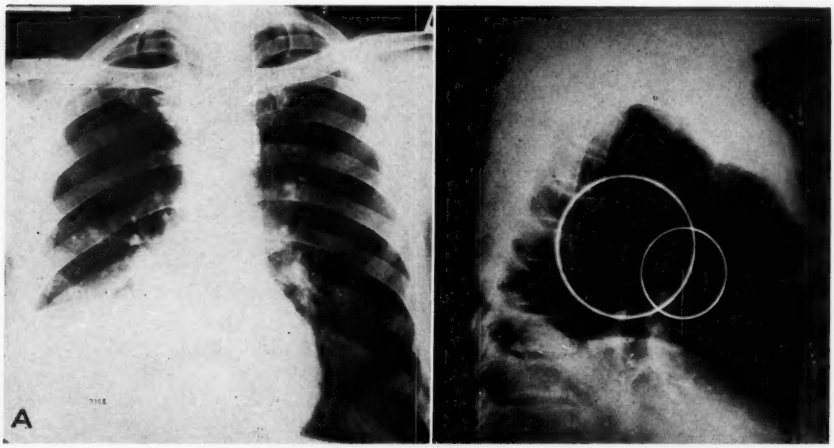

Fig. 4.—*A* and *B*, Posteroanterior and lateral radiographs of man aged 61, showing atelectasis of the right middle and lower lobes due to a tumor occluding the right main bronchus. The white circles are concerned with calculation of dose.

TABLE III. SURVIVAL RATES OF 148 PATIENTS WHO HAD A THORACOTOMY WITH OR WITHOUT HIGH-VOLTAGE RADIOTHERAPY (BROMPTON AND ROYAL MARSDEN HOSPITALS, 1951—1958)

	TOTAL PATIENTS IN GROUP	SURVIVAL RATES (LIFE-TABLE METHOD) (%)		
		6 MO.	1 YR.	2 YR.
Thoracotomy only	101	37	10	1
Squamous and adenocarcinoma	39*	41	8	–
Undifferentiated	43	35	12	–
Type unknown	19	–	–	–
Thoracotomy and high voltage radiotherapy †	47	71	19	6
Totals	148	48	13	2

*6 adenocarcinomas.

†8 squamous; 16 undifferentiated; 23 type unknown.

symptoms, and a few had some relief. The length of time before the symptoms recurred was variable, but at the moment 15 of the entire group are completely well and symptom free. Each of the symptoms which can be attributed to the local effects of carcinoma of the bronchus has been abolished completely or relieved at least temporarily. This includes such devastating symptoms as the pain of an apical tumor which has invaded the brachial plexus, and the effects of superior vena caval obstruction. Paralysis, resulting from pressure on the phrenic and recurrent laryngeal nerves, has been reversed, and such common symptoms as cough and hemoptysis are nearly always abolished. One patient, who was very ill from the toxic effects of a

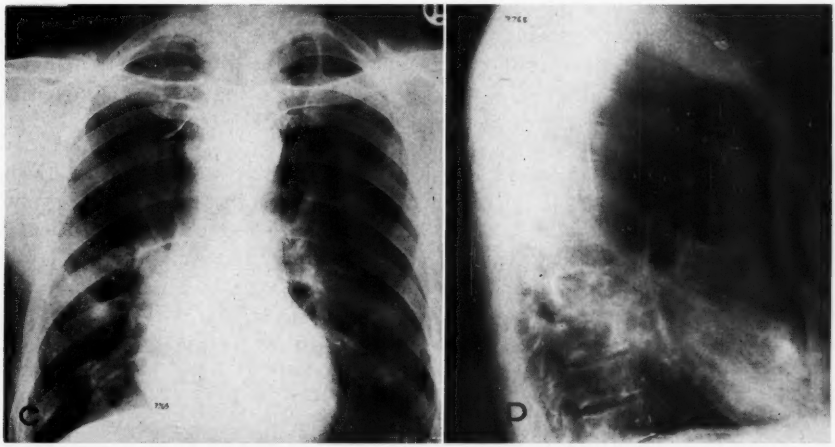

Fig. 4.—Cont'd. *C* and *D*, Similar films 4 months after endobronchial implantation. The lung has re-expanded.

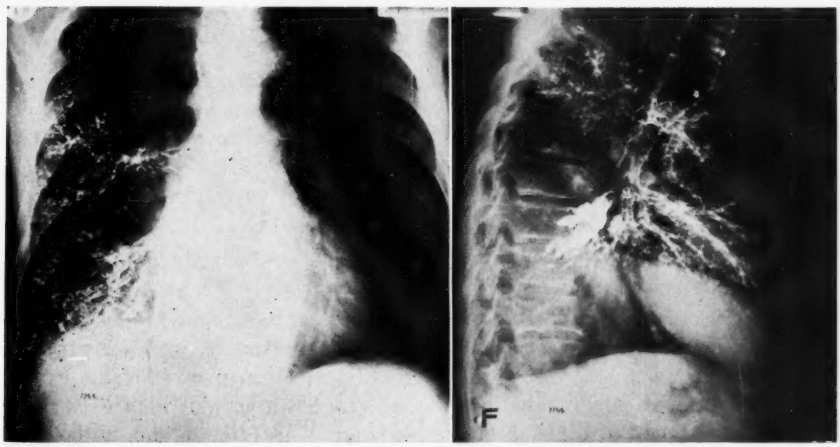

Fig. 4.—Cont'd. *E* and *F*, Posteroanterior and lateral bronchograms at the same stage. The right main bronchus is of normal caliber but there is a considerable degree of bronchiectasis in the lobes which were collapsed.

breaking-down carcinoma, had immediate and complete relief. An index of their general well-being and improvement is surely to be found in the fact that some two thirds of the patients gain weight, and the average gain is almost a stone.

Work.—Fifty-one patients who received a gold grain implant as the only treatment had been at work prior to their illness. After treatment, 18, or just over a third, were able to resume their employment for a time at least.

X-Ray Changes.—The x-ray appearance followed the clinical picture with reasonable accuracy. In a fifth of the patients the x-ray picture was restored to normal. In almost the same number there was a marked improvement, with almost complete resolution of the previous abnormality. In another third, there was a significant change for the better, but in the remainder there was no change. Figs. 2, 3, and 4 illustrate the changes which occurred in the chest x-ray appearance in 3 patients treated with interstitial irradiation.

Mode of Death.—It would be pleasing to be able to report that those patients who eventually die after this treatment do so in comfort, their symptoms having been relieved. Most of the deaths have occurred in the patients' homes, and the information available is unfortunately incomplete. There is the particular instance of a patient relieved of superior vena caval obstruction and dying without recurrence of this complication, but the bulk of the evidence which we have unfortunately points to the conclusion that the manner of dying is no different from that of untreated patients.

CONCLUSIONS

This is no more than a preliminary report of work done at a conservative dose level for a trial period. The number of patients is too small and the average follow-up period is too short to allow hard and fast conclusions to be drawn.

There is some slight evidence that these patients live a little longer than patients who are untreated, or who have thoracotomy alone, but as yet this is far from established. It is of some encouragement that 3 patients, in whom the only treatment has been radioactive gold grain implantation, have no evidence of recurrence after 2 years.

On the other hand, we feel that the evidence is conclusive that symptoms can almost always be relieved, so that the patient's general health is improved, and some are able to return to work.

We feel that the degree of symptomatic relief in so many, in conjunction with the apparent prolongation of life in several instances, justify continuing this form of treatment until a more accurate assessment of its value can be made. These patients, it must be remembered, are otherwise hopeless cases—the only treatment available is palliative external irradiation and, unlike gold grain implantation, this is very time consuming and disturbing to the patient.

For the future, it is intended to increase the level of dosage above 6,000 rads, as this can be done safely without tissue necrosis. In certain patients it may be advisable to supplement interstitial with external irradiation, making use of the information regarding the extent of the tumor which has been obtained at thoracotomy. Ideally, an isotope with half-life of about 10 days is needed, so that the implant could always be available and stored in the operating theatre.

We wish to thank Sir Clement Price Thomas and Mr. N. R. Barrett for permission to include their patients in this study. Prof. D. W. Smithers has given us constant help and invaluable advice and for this we are extremely grateful. We are indebted also to Dr. J. R. Bignall for his help and, in particular, for the useful comparison he has enabled us to make with patients who received external radiation, and with patients who had surgical exploration only.

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THE SOLITARY PULMONARY METASTASIS

An Appraisal of the Primary Site

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THE SOLITARY pulmonary lesion has long been difficult to diagnose. The ones which are metastatic represent a small per cent in various series of single lung tumors reported. An attempt has been made to survey the literature in order to present an adequate appraisal of the relative frequency with which primary neoplasms give rise to isolated metastatic lesions. It is hoped that systematic grouping of this information may be of value in management of the suspected solitary metastasis by leading to more accurate diagnosis and, as a result, better treatment for the patient.

The literature was carefully reviewed. Cases were selected for inclusion in this study only if all the following criteria were met: (1) solitary pulmonary metastatic lesion; (2) proved primary site; and (3) histologic proof of malignant neoplasm.

Many papers were studied, but only those which contained cases fulfilling the aforementioned criteria are listed in the bibliography. Some reports presented many more cases than those selected from them for inclusion here, but those which did not meet the criteria were omitted. Although a few cases listed here include lesions which were found to be multiple at the time of operation, the lesion was a solitary one as far as could be determined by preoperative clinical evaluation. This is to be expected and does not detract from the analysis.

The lesions are classified in "nodular," "infiltrative," or "not-stated" categories. The "infiltrative" group represents either segmental atelectasis or a pneumonic infiltration distal to bronchial obstruction, caused by a solitary mass. In the "not-stated" group, after careful review of each case, it was this author's opinion that the mass had been a single one, although the original contribution did not specify whether the lesion had been nodular or infiltrative.

Nomenclature of the histologic diagnosis has been followed as it appeared in the original paper, with one exception. "Melanosarcoma" has been changed to "malignant melanoma," as the nature of the neoplasm has now been clarified and it is regarded as a carcinoma. Malignant teratoma is regarded primarily as a carcinoma, although, on rare occasions, there may be sarcomatous changes in the malignant variety.

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Although pathologists tend to dislike the grouping of "carcinoma" versus "sarcoma" and prefer to describe soft tissue tumors according to the tissue from which the tumor-cell type is derived, for purposes of this analysis the simpler classification seems advisable. As this review includes reports dating back to 1930, some tumor nomenclature may not fit present diagnostic classifications. After careful study of each case report, this author was satisfied that all those used fulfilled the criteria.

Age and Sex.—The age was available for report in 118 cases; sex was given in 140 cases. Analysis reveals the average age of patients who had a solitary pulmonary metastasis was 48.4 years. The youngest patient was 13 years, the oldest 79. If the single malignant mass metastasized from carcinoma, the average age was 51.5 years; if from sarcoma, 35.5 years. Table I shows a breakdown into age groups.

TABLE I

AGE (YR.)	NUMBER OF CASES
11-20	7
21-30	13
31-40	19
41-50	17
51-60	32
61-70	26
71-80	4
Total	118

The sex incidence for all lesions was essentially equal, with 69 females and 71 males.

Type of Solitary Metastatic Pulmonary Lesion.—There were 101 single nodular metastases, 18 infiltrative lesions, and 100 lesions which were solitary but it was "not stated" as to which of the above categories they belonged. Of those cases in which the character of the lesion was clearly stated, the nodular type was most common.

Type of Primary Neoplasm.—There were 169 carcinomas and 50 sarcomas giving rise to a single pulmonary metastasis. As carcinomas are more common, Table II shows the breakdown of the primary site of carcinomas which gave rise to a solitary pulmonary metastasis.

Of the 169 carcinomas, 120 were adenocarcinoma, 18 were epidermoid carcinoma, and 31 were not classified in either group as they were mixed tumors, or specialized neoplasms, such as malignant melanoma or teratocarcinoma.

Table III shows the tabulation of soft tissue tumors. The neoplasms are listed by name as the primary site in the more common varieties is indicated in the name. The only "organ" sarcomas in this tabulation include three breast, two uterine, and one leiomyosarcoma of the jejunum.

An appraisal of the frequency of primary sites in all of the 219 cases is shown in Table IV.

DISCUSSION

This study indicates that a solitary pulmonary metastasis is most commonly nodular in character and arises from adenocarcinoma in a distant organ. There is no predilection for one sex and the age incidence represents the "cancer age" group.

These data would again emphasize careful preoperative evaluation of the solitary pulmonary nodule. One third (33 per cent) of these lesions, if metastatic, originate in the colon, rectum, and kidney. There are simple diagnostic procedures for screening these organs. Thorough physical examination, using the invaluable techniques of palpation and inspection wherever possible, may locate primary neoplasms in the testicle, breast, uterus, cervix, ovary, naso-oral cavity, thyroid, skin, salivary glands, and prostate. This group comprises more than one third (36.0 per cent) of the primary sites which produce single metastatic lesions in the lung. The high incidence of a solitary metastasis from carcinoma of the colon, rectum, and kidney may indicate that more aggressive surgical attack on these lesions should be pursued. Although such tumors as

TABLE II. CARCINOMA

PRIMARY SITE	NUMBER OF CASES	PER CENT
Colon (includes rectum)	40	24
Kidney	34	20
Testicle	14	8
Breast	12	7
Uterus	11	7
Melanoma	10	6
Naso-oral cavity	8	5
Ovary	7	4
Cervix	6	3
Stomach	5	3
Thyroid	5	3
Lung	4	2
Urinary bladder	3	2
Pancreas	3	2
Salivary gland	3	2
Prostate	2	1
Jejunum	1	0.5
Larynx	1	0.5
Total	169	100.0

TABLE III. SARCOMA

TYPE	NUMBER OF CASES	PER CENT
Osteogenic sarcoma	14	28
Fibrosarcoma	13	26
Chondrosarcoma	4	8
Angiosarcoma	4	8
Synovial sarcoma	3	6
Leiomyosarcoma	2	4
Rhabdomyosarcoma	2	4
Liposarcoma	1	2
Neurogenic sarcoma	1	2
Giant cell sarcoma (bone)	1	2
Ewing's sarcoma	1	2
"Sarcoma"	4	8
Total	50	100

TABLE IV. PRIMARY SITE OF 219 NEOPLASMS GIVING RISE TO A SOLITARY PULMONARY METASTASIS

PRIMARY SITE	NUMBER OF CASES	PER CENT
Colon	40	18
Cecum	(2)	
Colon	(19)	
Rectosigmoid	(6)	
Rectum	(13)	
Kidney	34	16
Breast	15	7
Testicle	14	6
Osteogenic sarcoma	14	6
Uterus	13	6
Fibrosarcoma	12	6
Malignant melanoma	10	5
Naso-oral cavity	8	4
Ovary	7	3
Cervix	6	3
Stomach	5	2
Thyroid	5	2
Lung	4	2
Chondrosarcoma	4	2
Angiosarcoma	4	2
Urinary bladder	3	1
Pancreas	3	1
Salivary gland	3	1
Synovial sarcoma	3	1
Prostate	2	1
Rhabdomyosarcoma	2	1
Jejunum	2	1
Larynx	1	0.5
Liposarcoma	1	0.5
Neurogenic sarcoma	1	0.5
Giant cell sarcoma (bone)	1	0.5
Ewing's sarcoma	1	0.5
"Sarcoma"	1	0.5
Total	219	100.0

pancreatic carcinoma and retroperitoneal sarcomas may defy detection, the majority of primary neoplasms are accessible for proper evaluation if methodical physical examination and commonly used diagnostic techniques are undertaken.

SUMMARY

1. The primary site of 219 malignancies giving rise to a solitary pulmonary metastasis is reported.

2. The average age of patients with a solitary pulmonary metastasis is 48.4 years and there is equal sex distribution.

3. A nodule is the most common type of single metastatic pulmonary lesion.

4. Adenocarcinomas are the most common neoplasms which produce a single metastatic lesion in the lung.

5. Most of the primary neoplasms giving rise to a solitary pulmonary metastasis arise in organs easily accessible to examination.

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SELECTIVE ISOLATED PERFUSION OF THE RIGHT OR LEFT LUNG

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THE INTRODUCTION of the principle of isolated organ perfusion opened a vast new area of treatment for patients with neoplastic disease. For utmost utilization of this therapeutic approach, a relatively easy and safe perfusion technique is essential for each organ or region of the body. Techniques have been employed clinically for perfusion of the brain, head and neck, liver, midgut, pelvis, and extremities.[1, 2, 4, 5, 6] Creech and his associates[2] described a method to accomplish simultaneous perfusion of both lungs via two extracorporeal pump-oxygenators. Clinically they reported encouraging results in the treatment of 3 patients by this procedure.

This study was undertaken to develop an effective method to perfuse selectively either the right or left lung.

METHOD

After a series of pilot experiments, the following techniques were devised.

Healthy adult mongrel dogs were anesthetized with intravenous pentobarbital, placed in the right lateral decubitus position, and positive pressure room air was administered through an endotracheal tube. The left pleural cavity was entered through the left fifth intercostal space. The pericardium was incised posterior and parallel to the left phrenic nerve and the left pulmonary artery, the pulmonary veins and lateral portion of left atrium were freed of their investing pericardium. The animal was heparinized with aqueous heparin, 1.5 mg. per kilogram of body weight. A bulldog clamp was placed on the left pulmonary artery at its origin, and, through a transverse arteriotomy just distal to the clamp, a flanged polyvinyl catheter was inserted into the pulmonary artery and secured with an umbilical tape snare. A Satinsky clamp was placed on the left atrium in such a manner that all blood returning from the left lung was isolated in the occluded segment of the left atrium and blood from the right lung was unimpeded in its flow through the mitral valve. A flanged polyvinyl catheter, 6 mm. in diameter, was inserted in the isolated segment of left atrium (Fig. 1).

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For perfusion of the right lung, the right pleural cavity was entered through a standard fifth intercostal incision. After the right pulmonary artery and veins were freed from the surrounding pericardium, Sondergaard's groove was carefully dissected. To facilitate securing an occlusive catheter in the right pulmonary artery, the azygos vein was divided near its junction with the superior vena cava. The pulmonary artery, as it passed beneath the right mainstem bronchus, was mobilized. A flanged polyvinyl catheter was inserted through a purse-string suture in the right ventricular outflow tract, threaded through the pulmonary conus into the right pulmonary artery, and secured proximal to the right upper lobe artery with an umbilical tape snare. A Satinsky clamp was placed on the left atrium as deep in the interatrial groove as possible. Blood from the right lung was isolated by this clamp without interfering with the venous return from the left lung (Fig. 2).

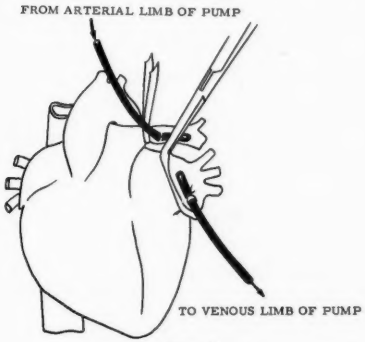

Fig. 1.

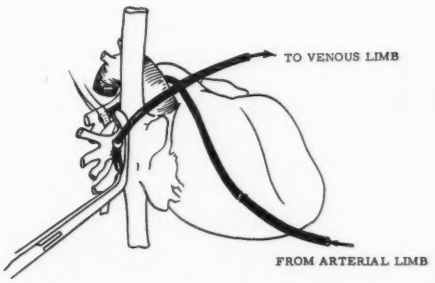

Fig. 2.

Fig. 1.—Schematic drawing showing the method used for perfusion of the left lung.
Fig. 2.—Schematic drawing showing the method used for perfusion of the right lung.

The blood drained by gravity from the left atrial cannula into a venous reservoir which contained 300 to 400 c.c. of heparinized blood exposed to atmospheric pressure. From the reservoir the blood passed through a single Sigmamotor pump into the arterial cannula. Extracorporeal oxygenation of the blood was not necessary as the positive pressure ventilation administered throughout the operative procedure oxygenated both the systemic and perfusion blood. Perfusion was continued at arterial flow rates of 140 c.c., 235 c.c., or 330 c.c. per minute for 20 to 30 minutes. Nitrogen mustard in a given concentration and a 5 c.c. aliquot of radioactive iodinated serum albumin were added to the reservoir. After completion of the perfusion, the catheters were removed, the atriotomy and arteriotomy closed with 5-0 arterial silk, and occluding clamps released. Heparin was neutralized with Polybrene and the wound closed in the standard manner.

Pulmonary arterial and venous pressures were recorded before and during the perfusion. Radioactivity counts of the perfused and systemic blood at the conclusion of perfusion and biweekly complete blood counts were determined to assess the escape of the perfusate into the general circulation. Lung biopsies were performed at intervals from the first to fifty-sixth postoperative day and at autopsy.

RESULTS

In 20 mongrel dogs, isolated perfusion of either the left or right lung was performed with the addition of nitrogen mustard in the concentration of 0.4 to 0.7 mg. per kilogram of body weight to the blood in the venous reservoir. Early in this series, operative errors resulted in the death of 3 animals (Table I). Three later deaths (fourth, sixth, and tenth postoperative days) occurred. In no case did death result from the dosage of the nitrogen mustard. Radioactivity

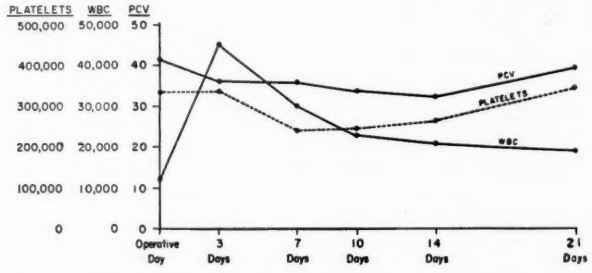

Fig. 3.—Graphic demonstration of the average hematologic values after selective lung perfusion with HN_2.

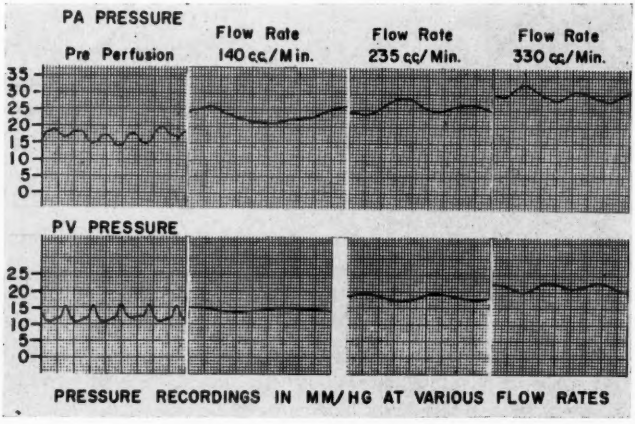

Fig. 4.—Actual pressure recordings during left lung perfusion at various flow rates per minute.

counts of the systemic and perfusion blood revealed the maximal leakage in any dog to be 2 per cent, with an average leakage into the systemic circuit of less than 0.5 per cent. Fig. 3 summarizes the hematologic changes after the perfusions; in no case was there evidence of hematopoietic depression. The differential counts revealed a shift to the left with the immediate postoperative leukocytosis and slow return to normal as the white blood cell counts fell to their preoperative levels. Fig. 4 is a representative tracing of arterial and venous pressures. Even with the higher flow rates when the venous pressure often rose

to 23 mm. Hg, pulmonary edema did not occur. Lung biopsies performed at intervals from the first to fifty-sixth day were normal, save a mild visceral pleuritis.

TABLE I. RESULTS OF LUNG PERFUSION WITH 0.4 TO 0.7 MG. PER KILOGRAM OF HN_2

3 Operative deaths:	1 anesthetic excess (pentobarbital)
	1 air embolism
	1 ventricular fibrillation
3 Late deaths:	2 pneumothorax (sixth-tenth day)
	1 empyema (fourth day)
14 Sacrificed	14 to 56 days after perfusion

In a second series of 16 dogs, perfusion of the lung was carried out with similar flow rates using HN_2 concentrations of 1.2 mg. to 3.5 mg. per kilogram of body weight (Table II). No deaths resulted with the concentration of HN_2 1.6 mg. per kilogram of body weight or less; there were no survivors at a HN_2 concentration of 1.7 mg. per kilogram of body weight or more. Fig. 5 shows the typical vascular effusion and pulmonary edema of local nitrogen mustard toxicity. Fig. 6 shows thickened alveolar septa after perfusion with large, but nonfatal doses of HN_2. In the 3 animals that received more than 1.7 mg. per kilogram of body weight of HN_2 and survived longer than 2 days, gross and microscopic examination of the perfused lungs revealed massive tissue necrosis and attempts at healing by fibrosis.

TABLE II. RESULTS OF LUNG PERFUSION WITH LARGE DOSES OF HN_2

DOG	KG. WT.	CONCENTRATION HN_2 (MG./KG.)	RESULT
897-D	9.0	1.2	Sacrificed 34th day; resolving pneumonia
742-D	16.5	1.2	Sacrificed 82nd day; minimal fibrosis
735-D	14.0	1.4	Sacrificed 84th day; minimal fibrosis
899-D	13.5	1.4	Sacrificed 30th day; resolving pneumonia
563-D	12.2	1.6	Sacrificed 85th day; minimal fibrosis
765-D	17.5	1.7	Died 21st day; marked fibrosis
721-D	16.0	1.9	Died 20th day; marked fibrosis
753-D	16.0	1.9	Died 1st day; hemorrhagic lung
700-D	16.0	1.9	Died 2nd day; hemorrhagic lung
748-D	15.0	2.0	Died 1st day; hemorrhagic lung
703-D	9.0	2.2	Died 2nd day; hemorrhagic lung
720-D	13.9	2.2	Died 1st day; hemorrhagic lung
709-D	14.5	2.8	Died 7th day; necrotic lung
643-D	17.2	2.9	Died 1st day; hemorrhagic lung
749-D	14.0	2.9	Died 1st day; hemorrhagic lung
752-D	11.3	3.5	Died 1st day; hemorrhagic lung

DISCUSSION

Pierpont and Blades[3] reported a method of perfusion of the left lung similar to the one herewith described. The major difference in these two methods is that in their method closed suction drainage was used to empty blood from the isolated atrial segment into a collecting venous reservoir. Only the volume of blood pumped from the venous reservoir was allowed to return to it. In this present study utilizing gravity drainage of the isolated atrial segments, the

Fig. 5.

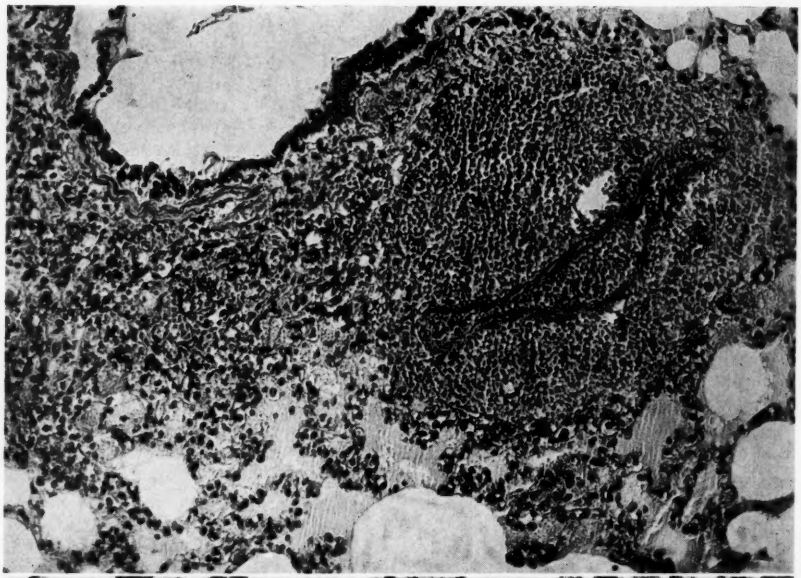

Fig. 6.

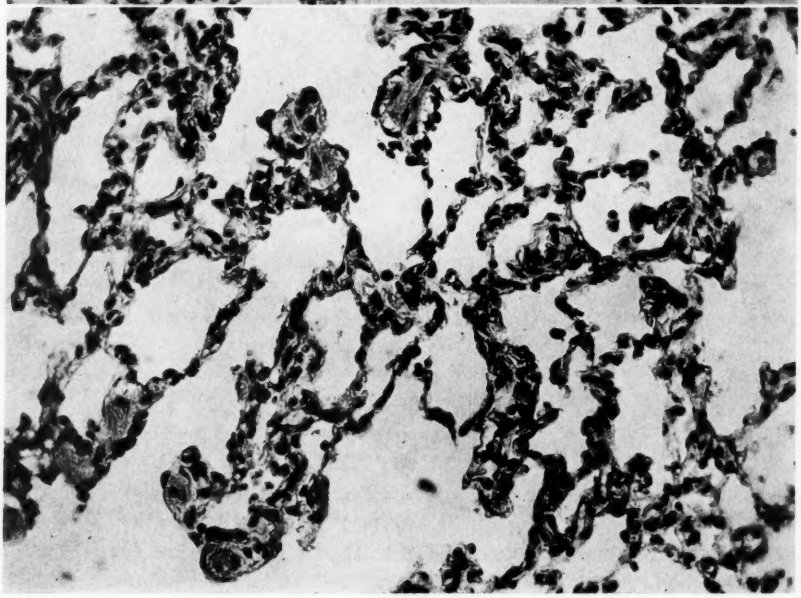

Fig. 5.—Photomicrograph of a lung biopsy at autopsy of an animal perfused with HN_2 in the concentration of 2.2 mg. per kilogram of body weight.

Fig. 6.—Photomicrograph of a lung biopsy 64 days after perfusion with HN_2 in the concentration of 1.4 mg. per kilogram of body weight. Note the thickened alveolar walls containing hyaline deposits.

blood level in the collecting reservoir did not remain stationary, but invariably rose during the course of the perfusion. The source of this additional blood must be the systemic circulation mediated through the bronchial arteries. If this additional blood volume is not allowed to leave the perfusion circuit and consequently must pool in the pulmonary capillary bed, an increased pulmonary vascular pressure results. This increased pressure added to the vascular effusion caused by nitrogen mustard in large doses, probably explains the inability of Pierpont and Blades to achieve survivors when concentrations of more than 0.4 mg. per kilogram of body weight of HN_2 were employed.

The histologic components of the lung allow easy investigation of pathologic changes occurring during perfusion. The local toxicity of HN_2 on the lung suggests that the usual perfusion concentration of HN_2 of 0.4 to 0.8 mg. per kilogram of body weight[2] is less than can be tolerated by normal body tissues. If the depressant effects of HN_2 on bone marrow are controlled by adequate isolation of the perfusion circuit or by a protective agent for the marrow, a concentration of HN_2 up to 1.6 mg. per kilogram may well be tolerated. The ability to detect accurately anatomic changes in lung tissue suggests further utilization of lung perfusion techniques for investigation of newer anti-neoplastic drugs.

The clinical application of these techniques is limited by the drugs presently available for organ perfusion. In certain clinical problems not amenable to conventional excisional therapy, isolated perfusion of either the right or left lung may be indicated. In pulmonary tumors involving the chest wall or vital structures of the thoracic inlet, in patients with multiple metastatic lesions in one lung, in pulmonary neoplastic disease after previous total removal of one lung, and in patients with long-standing chronic pulmonary insufficiency, selective isolated perfusion of either lung may be indicated.

SUMMARY

1. A safe and effective technique of selective isolated perfusion of either the left or right lung is presented.

2. Using this technique, isolated lung perfusion was performed in experimental animals with concentrations of nitrogen mustard up to 1.6 mg. per kilogram of body weight without adverse effect. There were no surviving animals when the mustard concentration was above this level.

3. The histologic components of the lung make pulmonary tissue an ideal site to study local drug toxicities of new agents.

4. The clinical application of this technique is discussed.

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THE USE OF A BYPASS SHUNT LINE WITH A DISC OXYGENATOR

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THERE are numerous techniques utilized today in connecting a patient to the extracorporeal circulation apparatus. We have found a very simple and safe method, with several advantages over the usual technique. This type of arrangement has been used in over 100 clinical cases with no difficulties arising referable to the shunt line or the type of connections described.

A shunt line is an integral part of the Mayo-Gibbon machine.[4] It is also an integral part of the extracorporeal apparatus utilized by the Craaford-Senning pump oxygenator,[2] and, more recently, has been included in the version of the disc oxygenator used by Dr. Gross.[3]

After the advantage of utilizing a shunt-line oxygenator had been observed with both the Mayo-Gibbon apparatus and the Craaford-Senning apparatus, it was suggested that such a shunt line might very wisely be utilized in the disc oxygenator setup.[1] After evaluating this technique in the experimental laboratory, we finally have settled on the type of connections and technique herein described. A series of drawings illustrate the various steps.

Fig. 1. The various tubing arrangement as it rests on the operating field is demonstrated. The venous line connects to the venous reservoir of the oxygenator, and the arterial line arises in the arterial end of the oxygenator. The shunt line contains a stopcock through which samples may be withdrawn, or by means of which drugs may be introduced into the extracorporeal circulation, and then carried on to the patient.

Fig. 2 demonstrates the position of occluding clamps during which time the heart-lung machine is primed with blood and slowly allowed to recirculate. During this time the discs are turning slowly, but no gas has been added to the oxygenator chamber. Blood flows through the arterial line to the shunt line, and back to the oxygenator via the venous line.

Fig. 3 indicates the position of clamps on the tubing after the femoral artery connector has been inserted. By elevating the line between the femoral artery

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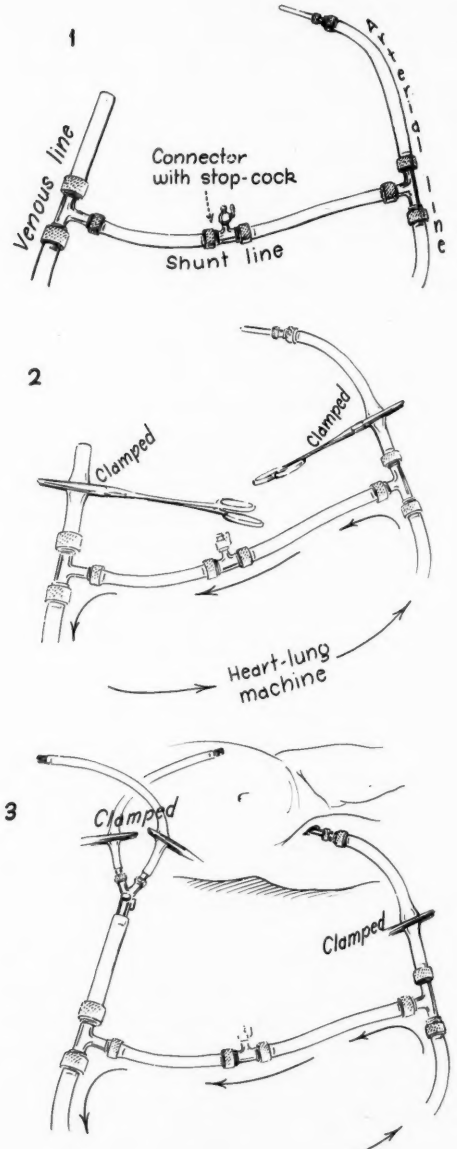

Fig. 1.—The venous tubing is ½ inch internal diameter, 3/32 inch wall. The shunt line and the arterial tubing is ⅜ inch internal 1/16 inch wall.

Fig. 2.—This figure indicates the direction of the recirculation. During this time, the pump is fully primed, dextrose solution is added as well as serum albumin.

Fig. 3.—The femoral artery cannula has been inserted. The arterial line is filled with blood, and the pump is allowed to continue to recirculate.

and the T-connector on the arterial line, and slowly releasing the clamp on the femoral artery line, blood flows back from the femoral artery into the shunt line, and all bubbles are easily evacuated into the shunt line and carried over to the venous end of the oxygenator. This step, in itself, has made cannulation considerably easier without the worry of bubbles existing in the arterial line. The superior vena cava and inferior vena cava cannulas are then inserted, and the gas is turned on filling the oxygenator chamber. The discs are then set to the desired rate. The arterial pump is turned up to produce, in the shunt line, and, consequently, in the venous flow line, the rate of flow expected or desired in this particular patient.

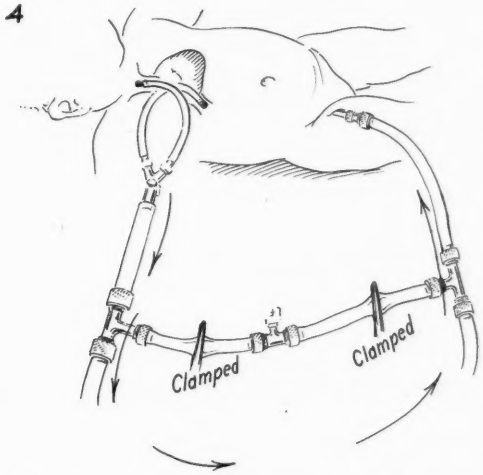

Fig. 4.—The inferior vena cava cannula is inserted first, and then the superior vena cava cannula. The siphon effect of the venous line is sufficient to fill the entire venous line when the clamps are released.

Fig. 4 indicates the position of the clamps after the caval cannulas have been inserted. The arterial clamps and venous clamps are removed and placed on the shunt line, placing the patient on a period of partial perfusion for a few moments. The tapes are then pulled up around the caval cannula, and the patient is on full perfusion.

The arterial pump is then adjusted to meet the venous return. The venous return then equals the arterial flow. To adjust flow rate, if it is desired to increase it, blood is added to the oxygenator. If it is desired to decrease the flow rate, blood is detracted from the oxygenator. Relatively small volumes of blood, either added to the patient or taken from the patient, will cause a rather significant change in blood flow, and consequently venous return. Should air enter the venous line, and destroy the negative pressure from the siphon, it is a simple matter to release the shunt-line clamps for a few seconds and refill the venous line, thus establishing the negative pressure. If air bubbles should ap-

pear in the arterial line, and in our experience this has never happened, a few seconds of shunt-line flow pass these air bubbles into the venous side where they will be swept into the venous reservoir.

After the operative procedure has been completed, it is quite easy now to go on partial perfusion, by clamping the superior caval cannula and removing it. The inferior caval cannula is then withdrawn until it rests within the right auricle. A small screw clamp is placed on the inferior vena cava cannula tube

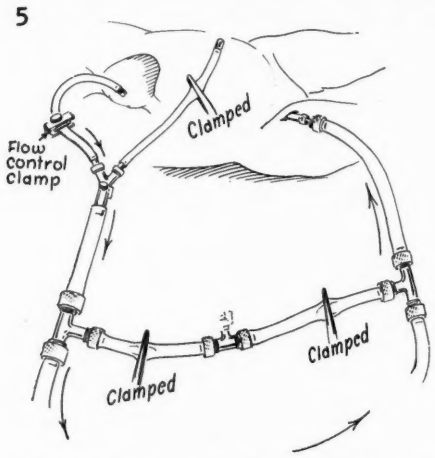

Fig. 5.—The intercardiac surgical procedure has been completed. The patient is now on partial perfusion. The flow control clamp is slowly closed. The pump speed is adjusted to correspond to venous return.

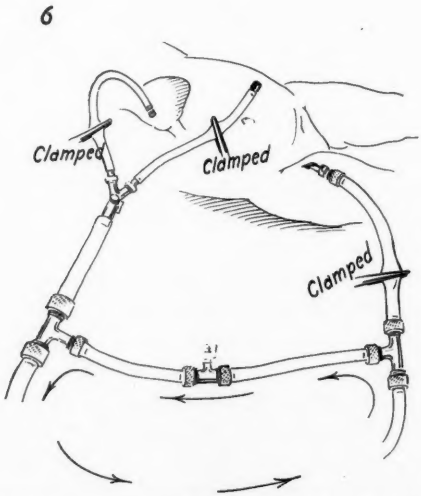

Fig. 6.—The inferior vena cava cannula still rests within the right auricle, and momentarily is clamped off to determine the ability of the heart to take over the full circulation.

decreasing the return to the oxygenator, and allowing the heart to take over more and more of the circulation. As the clinical situation indicates, the patient is gradually and progressively removed from partial perfusion.

Fig. 6 indicates the position of the clamps which we utilize to determine whether the patient can safely be removed from perfusion. The vena cava cannula is clamped off, the femoral artery cannula is clamped, and blood continues to recirculate through the shunt line. The pump operator has to make no adjustments at all for this flow. If the clinical situation indicates that a longer

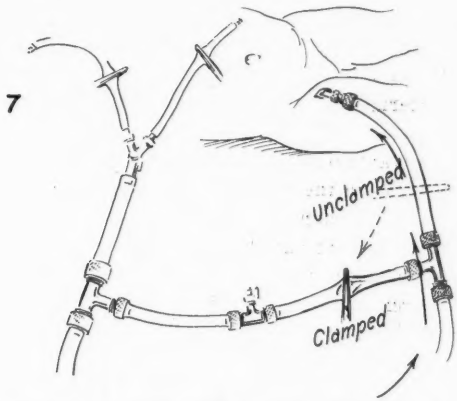

Fig. 7.—Both caval cannulas are removed and clamped. Clamp is released from the arterial line and placed on the shunt line while the patient is transfused with small amounts.

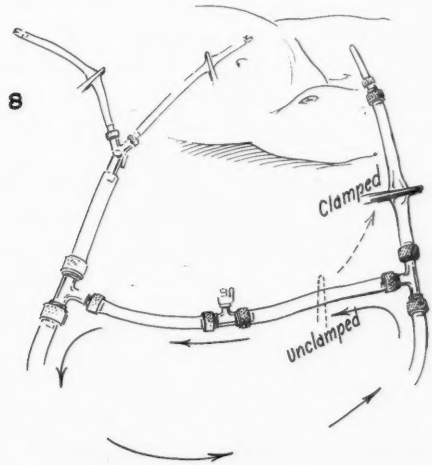

Fig. 8.—The clamp is reapplied to the arterial line. The femoral artery cannula is removed. The pump continues to recirculate until we are absolutely sure there is not indications to go back on perfusion. Pressures are measured in all chambers of the heart to determine the degree of correction of the defect. If, for any reason, it is considered that further surgery is indicated, the cannulas are all reinserted and perfusion is reinstituted.

period of partial perfusion is warranted, clamps are simply removed from the arterial line and the caval tube, and placed on the shunt line as indicated in Fig. 5, thereby placing the patient back on partial perfusion. The pump-oxygenator operator is often not aware of the transfer from partial perfusion to no perfusion except that he may notice blood returning from the venous tubing as bright red, and the shunt line is open.

Fig. 7 indicates the technique utilized to transfuse blood from the oxygenator to the patient, should blood balance indicate that the patient needs additional transfusion. The pump is slowly recirculating blood through the shunt line. The shunt line is clamped (Fig. 8). Blood flows into the patient. When sufficient transfusion has occurred, the arterial line is again clamped, and blood recirculates through the shunt line. The clamp is then taken from the shunt line and placed on the arterial line. The femoral artery cannula is completely removed.

One of the real advantages of this arrangement for us has been that there need be no exchange between the surgical team and the pump operating team in order to go on and off perfusion. It puts the control of full perfusion, partial perfusion, or no perfusion in the hands of the surgical team.

This same arrangement is applicable to left atrial femoral artery bypass for aneurysmal or aortic arch surgery. In this situation, the reservoir is usually inserted in the left atrial line.

SUMMARY

We have indicated the technique and advantages which we believe are desirable in the utilization of a bypass shunt line with a disc oxygenator. Such a shunt line is, of course, applicable to any pump oxygenator. We feel that these techniques described have allowed us to place patients on perfusion and terminate the perfusion more easily than with techniques previously used.

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THE MANAGEMENT OF VENTRICULAR FIBRILLATION AFTER INDUCED CARDIAC ARREST

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INCREASING experience with open-heart surgery has shown that induced cardiac arrest facilitates the repair of many intracardiac defects. When the heart is allowed to recover from induced arrest, ventricular fibrillation may result. Continued coronary perfusion usually allows defibrillation to occur, either spontaneously or after electric shock. However, certain conditions can make defibrillation difficult or impossible to achieve. It is the purpose of this communication to describe a technique which has been found useful in such circumstances.

The hazards of unrelieved left heart distention while the heart is arrested have been recognized and described by several investigators.[1, 2] As a result, left heart decompression is almost routine when induced cardiac arrest is contemplated in open-heart surgery. When induced cardiac arrest is employed in patients undergoing aortic valve surgery, post-arrest fibrillation is particularly difficult to eliminate, even although left atrial drainage has been utilized. Clauss and associates[3] have shown this to be secondary to a degree of residual aortic regurgitation. The unremitting pressure of the pump-oxygenator exerted through an incompetent aortic valve results in an elevated end-diastolic pressure in the left ventricle. Such a situation may preclude successful defibrillation.

Three cases have been encountered at the Vancouver General Hospital in which defibrillation was impossible until a simple modification in the bypass procedure resulted in successful cardiac resuscitation. The first of these cases was a 14-year-old boy with a ventricular septal defect and aortic regurgitation secondary to prolapse of an aortic leaflet. Under total cardiac bypass, with arrest induced by potassium citrate, the septal defect was closed and an attempt was made to reconstitute the aortic valve. When the clamp was removed from the aorta, marked left heart dilatation occurred, together with ventricular fibrillation. This was before the value of left heart decompression had been recognized, and a left atrial cannula was not used. When the heart was decompressed by massage, repeated attempts at electrical defibrillation were

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unsuccessful. Almost in desperation the pump-oxygenator was stopped with the hope that the decrease in pressure on the left ventricle would allow defibrillation. Electric shock was then immediately successful in restoring an effective ventricular beat. Subsequently, the patient's circulation was well maintained, even though a considerable degree of aortic regurgitation persisted.

This experience has been repeated subsequently in 2 patients after repair of calcific aortic stenosis. In 1 of these cases the heart had been arrested with potassium citrate and in the other with myocardial hypothermia. Left atrial decompression was utilized in both instances but, despite this, defibrillation could not be achieved until the pump was stopped. Then electrical defibrillation was immediately successful, and satisfactory cardiac action persisted.

DISCUSSION

It would appear that residual aortic regurgitation will permit the pressure generated by the pump-oxygenator to be exerted into the left ventricular cavity. This keeps the end-diastolic pressure at abnormally high levels and at these levels resuscitation of the fibrillating ventricle may be impossible. The apparently drastic measure of discontinuing total body perfusion may be necessary to reduce the end-diastolic pressure in the left ventricle to a level compatible with defibrillation. In the cases mentioned, adequate cardiac output has resumed in time to avoid the effects of inadequate body perfusion.

SUMMARY

When resistant ventricular fibrillation occurs in patients on cardiac bypass, after intracardiac surgery, it may be necessary to stop the pump-oxygenator to effect defibrillation.

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Announcement

THE AMERICAN ASSOCIATION FOR THORACIC SURGERY

Notice of Annual Meeting

The Forty-second Annual Meeting of The American Association for Thoracic Surgery will be held April 16, 17, and 18, 1962, in St Louis, Missouri. Headquarters will be The Chase-Park Plaza Hotels.

Requests for Hotel Reservations

These should be mailed directly to Mr. T. J. Robinson, Executive Assistant Manager, The Chase-Park Plaza Hotels, St. Louis 8, Missouri. Please mention this Association, the type of accommodation desired, the date, and approximate hour of arrival and departure. If accommodations are desired elsewhere please communicate directly with the hotel of your choice.

Material for the Program

SCIENTIFIC PAPERS.—Abstracts of all papers proposed for presentation at the 1962 meeting *must be received on or before* **November 15, 1961,** otherwise they will not be considered by the Program Committee. These should contain *not more than* **200** *words* that accurately and clearly reflect the content of the completed paper. They should be labeled "For Thoracic Surgery Forum" or "For Regular Program," depending upon the nature of the subject matter. The Forum is primarily for the presentation of short papers on current thoracic research, experimental problems, anatomical studies, and modified or new surgical techniques.

Six, repeat, six clearly legible copies of each abstract must be sent to Miss Ada Hanvey, Administrative Assistant, The American Association for Thoracic Surgery, Suite 311 Carondelet West, 7730 Carondelet Avenue, St. Louis 5, Missouri.

Essayists selected for the program are reminded that papers presented at the meeting are to be published in the Journal and *must* be handed to the secretary *immediately* after their presentation. The maximum length allowed for Forum papers is 3,000 words without illustration. If illustrated, an appropriate number of words must be subtracted.

Applications for Membership

Applications for Associate Membership in the Association must be received by the Membership Committee *not later than* **November 15, 1961,** otherwise the application will be deferred for consideration until the 1963 meeting.

Applicants must be sponsored by three Active or Senior Members of the Association. In addition to the signature on the application form, the sponsors will forward a *separate* letter concerning the applicant directly to:

Charles K. Kirby, M.D.
Chairman of the Membership Committee
3400 Spruce Street
Philadelphia 4, Pennsylvania

Sponsors are reminded that *new* letters of recommendation must be forwarded to the Chairman of the Membership Committee should their applications be held over for reconsideration a *second year.*